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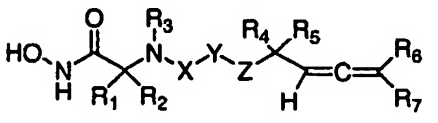
(54) Title: ALLENIC ARYL SULFONAMIDE HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASE AND TACE INHIBITORS



(I)

(57) Abstract: Compounds of the formula (I) are useful in treating disease conditions mediated by TNF-α, such as rheumatoid arthritis, osteoarthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease, degenerative cartilage loss, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease and HIV.

ALLENIC ARYL SULFONAMIDE HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASE AND TACE INHIBITORS

FIELD OF INVENTION

This invention relates to allenic aryl sulfonamide hydroxamic acids which act as inhibitors of TNF-α converting enzyme (TACE) and matrix metalloproteinase (MMP). The compounds of the present invention are useful in disease conditions mediated by MMP and TACE, such as rheumatoid arthritis, osteoarthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease, degenerative cartilage loss, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease and HIV.

BACKGROUND OF THE INVENTION

TNF-α converting enzyme (TACE) catalyzes the formation of TNF-α from membrane bound TNF-α precursor protein. TNF-α is a pro-inflammatory cytokine that is believed to have a role in rheumatoid arthritis [Shire, M. G.; Muller, G. W. *Exp. Opin. Ther. Patents* 1998, *8(5)*, 531; Grossman, J. M.; Brahn, E. *J. Women's Health* 1997, *6(6)*, 627; Isomaki, P.; Punnonen, J. *Ann. Med.* 1997, *29*, 499; Camussi, G.; Lupia, E. *Drugs*, 1998, *55(5)*, 613.] septic shock [Mathison, *et. al. J. Clin. Invest.* 1988, *81*, 1925; Miethke, *et. al. J. Exp. Med.* 1992, *175*, 91.], graft rejection [Piguet, P. F.; Grau, G. E.; *et. al. J. Exp. Med.* 1987, *166*, 1280.], cachexia [Beutler, B.; Cerami, A. *Ann. Rev. Biochem.* 1988, *57*, 505.], anorexia, inflammation [Ksontini, R,; MacKay, S. L. D.; Moldawer, L. L. *Arch. Surg.* 1998, *133*, 558.], congestive heart failure [Packer, M. *Circulation*, 1995, *92(6)*, 1379; Ferrari, R.; Bachetti, T.; et. al. *Circulation*, 1995, *92(6)*, 1479.], post-ischaemic reperfusion injury, inflammatory disease of the central nervous system, inflammatory bowel disease, insulin resistance [Hotamisligil, G. S.; Shargill, N. S.; Spiegelman, B. M.; *et. al. Science*, 1993, *259*, 87.] and HIV infection [Peterson, P. K.; Gekker, G.; *et. al. J. Clin. Invest.* 1992, *89*, 574; Pallares-Trujillo, J.; Lopez-Soriano, F. J. Argiles, J. M. *Med. Res.*

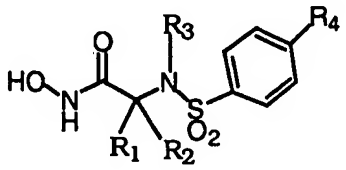
Reviews, 1995, *15(6)*, 533.]], in addition to its well-documented antitumor properties [Old, L. *Science*, 1985, *230*, 630.]. For example, research with anti-TNF-αntibodies and transgenic animals has demonstrated that blocking the formation of TNF-α inhibits the progression of arthritis [Rankin, E.C.; Choy, E.H.; Kassimos, D.; Kingsley, G.H.; Sopwith, A.M.; Isenberg, D.A.; Panayi, G.S. *Br. J. Rheumatol.* 1995, *34*, 334; *Pharmaprojects*, 1996, Therapeutic Updates *17 (Oct.)*, au197-M2Z.]. This observation has recently been extended to humans as well as described in "TNF-α in Human Diseases", *Current Pharmaceutical Design*, 1996, *2*, 662.

Matrix metalloproteinases (MMPs) are a group of enzymes that have been implicated in the pathological destruction of connective tissue and basement membranes. These zinc containing endopeptidases consist of several subsets of enzymes including collagenases, stromelysins and gelatinases. Of these classes, the gelatinases have been shown to be the MMPs most intimately involved with the growth and spread of tumors. It is known that the level of expression of gelatinase is elevated in malignancies, and that gelatinase can degrade the basement membrane which leads to tumor metastasis. Angiogenesis, required for the growth of solid tumors, has also recently been shown to have a gelatinase component to its pathology. Furthermore, there is evidence to suggest that gelatinase is involved in plaque rupture associated with atherosclerosis. Other conditions mediated by MMPs are restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neo-vascularization and corneal graft rejection. For recent reviews, see: (1) Recent Advances in Matrix Metalloproteinase Inhibitor Research, R. P. Beckett, A. H. Davidson, A. H. Drummond, P. Huxley and M. Whittaker, Research Focus, Vol. 1, 16-26, (1996), (2) Curr. Opin. Ther. Patents (1994) 4(1): 7-16, (3) Curr. Medicinal Chem. (1995) 2: 743-762, (4) Exp. Opin. Ther. Patents (1995) 5(2):

1087-110, (5) Exp. Opin. Ther. Patents (1995) 5(12): 1287-1196: (6) Exp. Opin. Ther. Patents (1998) 8(3): 281-259.

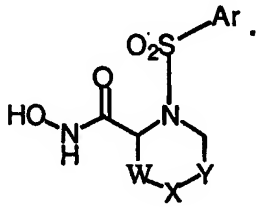
It is expected that small molecule inhibitors of TACE would have the potential for treating a variety of disease states. Although a variety of TACE inhibitors are known, many of these molecules are peptidic and peptide-like which suffer from bioavailability and pharmacokinetic problems. In addition, many of these molecules are non-selective, being potent inhibitors of matrix metalloproteinases and, in particular, MMP-1. Inhibition of MMP-1 (collagenase 1) has been postulated to cause joint pain in clinical trials of MMP inhibitors [*Scrip*, 1998, *2349*, 20] Long acting, selective, orally bioavailable non-peptide inhibitors of TACE would thus be highly desirable for the treatment of the disease states discussed above.

U. S. patents 5,455,258, 5,506,242, 5,552,419, 5,770,624, 5,804,593, and 5,817,822 as well as European patent application EP606,046A1 and WIPO international publications WO9600214 and WO9722587 disclose non-peptide inhibitors of matrix metalloproteinases and/or TACE of which the aryl sulfonamide hydroxamic acid shown below is representative. Additional publications disclosing sulfonamide based MMP inhibitors which are variants of the sulfonamide-hydroxamate shown below, or the analogous sulfonamide-carboxylates, are European patent applications EP-757037-A1 and EP-757984-A1 and WIPO international publications WO9535275, WO9535276, WO9627583, WO9719068, WO9727174, WO9745402, WO9807697, WO9831664, WO9833768, WO9839313, WO9839329, WO9842659 and WO9843963. The discovery of this type of MMP inhibitor is further detailed by MacPherson, *et. al.* in *J. Med. Chem.*, 1997, *40*, 2525 and Tamura, *et. al.* in *J. Med. Chem.* 1998, *41*, 640.

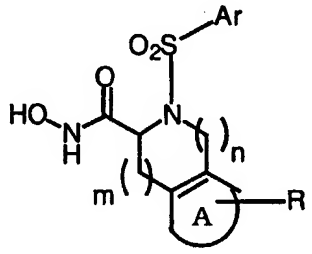


Publications disclosing β-sulfonamide-hydroxamate inhibitors of MMPs and/or TACE in which the carbon alpha to the hydroxamic acid has been joined in a ring to the sulfonamide nitrogen, as shown below, include U. S. patent 5,753,653, WIPO

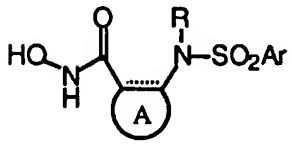
international publications WO9633172, WO9720824, WO9827069, WO9808815, WO9808822, WO9808823, WO9808825, WO9834918, WO9808827, Levin, *et. al. Bioorg. & Med. Chem. Letters* 1998, *8*, 2657 and Pikul, *et. al. J. Med. Chem.* 1998, *41*, 3568.



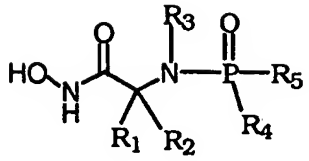
The patent applications DE19,542,189-A1, WO9718194, and EP803505 disclose additional examples of cyclic sulfonamides as MMP and/or TACE inhibitors. In this case the sulfonamide-containing ring is fused to a aromatic or heteroaromatic ring.



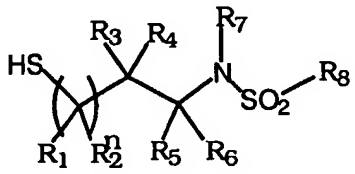
Examples of sulfonamide hydroxamic acid MMP/TACE inhibitors in which a 2 carbon chain separates the hydroxamic acid and the sulfonamide nitrogen, as shown below, are disclosed in WIPO international publications WO9816503, WO9816506, WO9816514 and WO9816520.



Analogous to the sulfonamides are the phosphinic acid amide hydroxamic acid MMP/TACE inhibitors, exemplified by the structure below, which have been disclosed in WIPO international publication WO9808853.



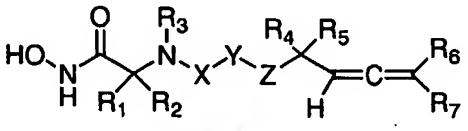
Sulfonamide MMP/TACE inhibitors in which a thiol is the zinc chelating group, as shown below, have been disclose in WIPO international application 9803166.



It is an object of this invention to provide aryl sulfonamide hydroxamic acid MMP/TACE inhibitors in which the sulfonyl aryl group is para-substituted with a substituted allenic moiety.

SUMMARY OF THE INVENTION

The invention provides TACE and MMP inhibitors of Formula (I):



(I)

wherein:

X is -S-, -SO-, -SO_2- or -P(O)-R_8;

Y is aryl or heteroaryl, with the proviso that X and Z may not be bonded to adjacent atoms of Y;

Z is -O-, -NH-, -CH_2- or -S-;

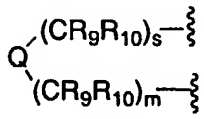
R_1 is hydrogen, aryl, heteroaryl, C_5-C_8 cycloheteroalkyl, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, or alkynyl of 2 to 6 carbon atoms;

R_2 is hydrogen, aryl, heteroaryl, cycloalkyl of 3 to 6 carbon atoms, C_5-C_8 cycloheteroalkyl, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, or alkynyl of 2 to 6 carbon atoms;

R_1 and R_2, taken together with the atoms to which they are attached, may form a 3 to 7 membered cycloalkyl or cycloheteroalkyl ring, which are as herein below defined;

R_3 is hydrogen, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, or alkynyl of 2 to 6 carbon atoms;

or R_1 and R_3, together with the atoms to which they are attached, may form a 5 to 8 membered ring wherein R_1 and R_3 represent divalent moieties of the formulae: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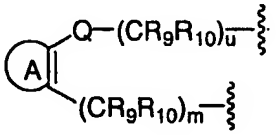
and


A is aryl or heteroaryl;
Q is a C-C single or double bond, -O-, -S-, -SO-, -SO_2-, -NR_{11}, or -$CONR_{12}$;
s is an integer of 0 to 3;
u is an integer of 1 to 4;
m is an integer of 1 to 3;

R_4 and R_5 are each, independently, hydrogen or alkyl of 1 to 6 carbon atoms;
R_6 and R_7 are each, independently, hydrogen, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, aryl, heteroaryl or cycloheteroalkyl;
or R_6 and R_7, together with the atom to which they are attached, may form 3 to 7 membered cycloalkyl or cycloheteroalkyl ring;

R_8 is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, aryl or heteroaryl;

R_9 and R_{10} are each, independently, selected from H, $-OR_{13}$, $-NR_{13}R_{14}$, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, aryl, heteroaryl, $-COOR_{13}$; or $-CONR_{13}R_{14}$; or R_9 and R_{10} taken together form a C_3-C_6-cycloalkyl of 3 to 6 carbon atoms or a cycloheteroalkyl ring; or R_9 and R_{10} taken together with the carbon to which they are attached, form a carbonyl group;

R_{11} is hydrogen, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, cycloheteroalkyl of 3 to 6 carbon atoms, aryl, heteroaryl, $-S(O)_nR_{13}$, $-COOR_{13}$, $-CONR_{13}R_{14}$, $-SO_2NR_{13}R_{14}$ or $-COR_{13}$, and n is an integer of 0 to 2;

R_{12} is hydrogen, aryl, heteroaryl, alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms; and

R_{13} and R_{14} are each, independently, hydrogen, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, aryl, heteroaryl or cycloheteroalkyl;

or a pharmaceutically acceptable salt thereof.

In the compound of this invention:

An example of Y is aryl, e.g. phenyl, such as where X and Z are positioned 1,4.

X may be for example $-SO_2-$.

An example of Z is oxygen.

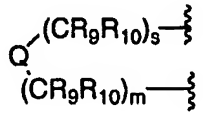
R_4 and R_5 may each be for example hydrogen.

R_6 may be for example hydrogen.

Examples of R_7 are hydrogen and methyl.

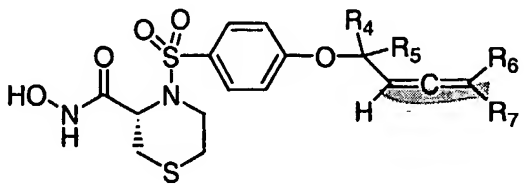
In some embodiments R_2 may be hydrogen or isopropyl. In some embodiments R_1 and R_3 may each be hydrogen.

Examples of R_1 and R_3 taken together are divalent moieties of the formula:

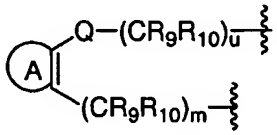


;

wherein Q is S. Examples of s and m are 2, e.g. where R_1 and R_3 taken together with the nitrogen to which they are attached form a thiomorpholine ring. The absolute stereochemistry may be for example as shown by the formula:



Other examples of R_1 and R_3 taken together are divalent moieties of the formula:



;

wherein Q is NR_{11} , and u and m are 1 and A is aryl such as phenyl.
Examples of R_9 and R_{10} are hydrogen.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Preferred compounds of this invention are those of Formula (I) in which Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, or a pharmaceutically acceptable salt thereof.

More preferred compounds of this invention are those of Formula (I) in which Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, X is SO_2, or a pharmaceutically acceptable salt thereof.

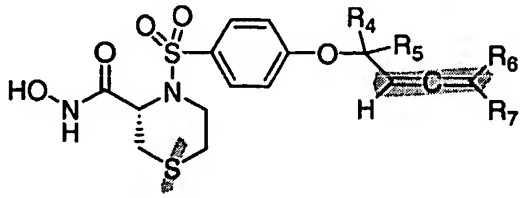
More preferred compounds of this invention are those of Formula (I) in which Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, X is SO_2, Z is oxygen.

More preferred compounds of this invention are those of Formula (I) in which Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, X is SO_2, Z is oxygen and R_4, R_5, and R_6 are hydrogen.

More preferred compounds of this invention are those of Formula (I) in which Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, X is SO_2, Z is oxygen, R_4, R_5, and R_6 are hydrogen, and R_7 is H or methyl.

More preferred compounds of this invention are those of Formula (I) in which Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, X is SO_2, Z is oxygen, R_2, R_4, R_5, and R_6 are hydrogen, and R_7 is H or methyl, R_1 and R_3, together with the atoms to which they are attached, form a thiomorpholine ring.

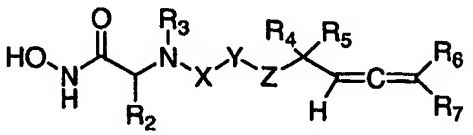
More preferred compounds of this invention are those of Formula (I) in which Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, X is SO_2, Z is oxygen, R_2, R_4, R_5, and R_6 are hydrogen, and R_7 is H or methyl, R_1 and R_3, together with the atoms to which they are attached, form a thiomorpholine ring such that Formula (I) has the absolute stereochemistry shown above, or a pharmaceutically acceptable salt thereof.



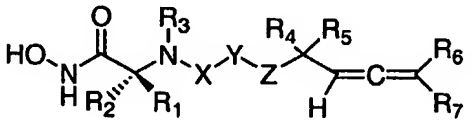
More preferred compounds of this invention are those of Formula (I) in which Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, X is SO_2, Z is oxygen, R_4, R_5, and R_6 are hydrogen, R_7 is H or methyl, and R_3 is H or methyl.

More preferred compounds of this invention are those of structure Formula (I) in which Y is a phenyl ring substituted at the 1- and 4-positions by X and Z,

respectively, X is SO_2, Z is oxygen, R_4, R_5, and R_6 are hydrogen, R_7 and R_3 is H or methyl, and R_2 is isopropyl as shown below.



More preferred compounds of this invention are those of Formula (I) in which Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, X is SO_2, Z is oxygen, R_4, R_5, and R_6 are hydrogen, R_7 and R_3 is H or methyl, R_2 is isopropyl, and R_1 is hydrogen, such that these compounds have the D-configuration, as shown below:

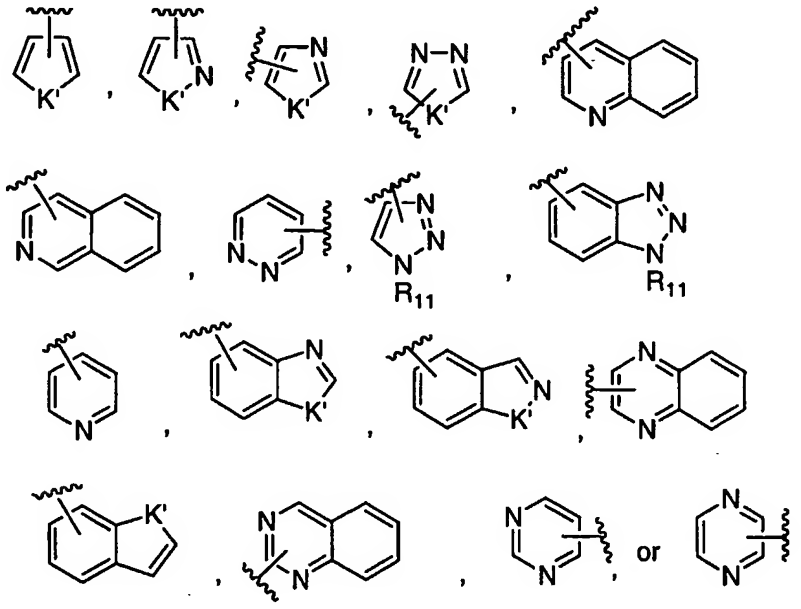


Among the specifically preferred compounds of this invention according to Formula (I) are the following compounds or pharmaceutically acceptable salts thereof:

2-({[4-(2,3-Butadienyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-methylbutanamide,
2-[{[4-(2,3-Butadienyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxy-3-methylbutanamide,
N-Hydroxy-3-methyl-2-({[4-(2,3-pentadienyloxy)phenyl]sulfonyl}amino)butanamide,
N-Hydroxy-3-methyl-2-(methyl{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}amino)butanamide,
(3S)-4-{[4-(2,3-Butadienyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide,
(3S)- N-Hydroxy-2,2-dimethyl-4-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-3-thiomorpholinecarboxamide,
1-Acetyl-4-{[4-(2,3-butadienyloxy)phenyl]sulfonyl}-N-hydroxy-2,3,4,5-tetrahydro-1H-1,4- benzodiazepine-3-carboxamide,

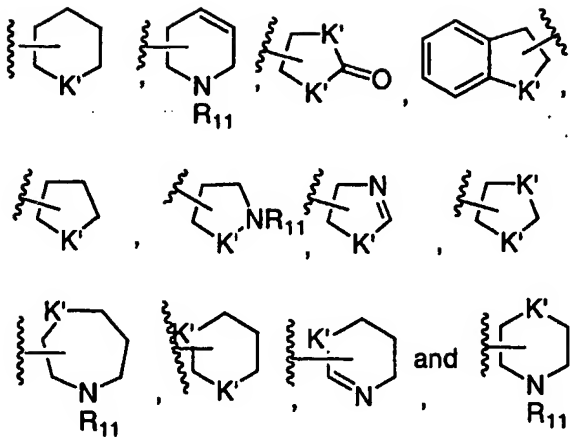
1-Benzoyl-4-(4-buta-2,3-dienyloxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-3-carboxylic acid hydroxyamide and 1-Benzoyl-N-hydroxy-4-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-3-carboxamide.

Heteroaryl, as used throughout, is a 5 to 10 membered mono- or bicyclic ring having from 1 to 3 heteroatoms selected from -N-, -NR_{11}, -S- and -O-. Heteroaryl is preferably



wherein K' is -O-, -S- or –NR_{11} and -R_{11} is as hereinabove defined. Preferred heteroaryl rings include pyrrole, furan, thiophene, pyridine, pyrimidine, pyridazine, pyrazine, triazole, pyrazole, imidazole, isothiazole, thiazole, isoxazole, oxazole, indole, isoindole, benzofuran, benzothiophene, quinoline, isoquinoline, quinoxaline, quinazoline, benzotriazole, indazole, benzimidazole, benzothiazole, benzisoxazole, and benzoxazole. Heteroaryl groups may optionally be mono or disubstituted.

Cycloheteroalkyl as used herein refers to a 5 to 8 membered saturated or unsaturated mono or bi-cyclic ring having 1 or 2 heteroatoms independently selected from -N-, -NR_{11}, -S- or -O-. Heterocycloalkyl rings of the present invention are preferably selected from;



wherein K' is $-NR_{11}$, -O- or -S- and $-R_{11}$ is as hereinabove defined. Preferred cycloheteroalkyl rings include piperidine, piperazine, morpholine, tetrahydropyran, tetrahydrofuran or pyrrolidine. Cycloheteroalkyl groups of the present invention may optionally be mono- or disubstituted.

Aryl, as used herein refers to a phenyl or naphthyl rings which may, optionally be mono-, di- or tri-substituted.

Alkyl means a straight or branched chain saturated aliphatic hydrocarbon radical of 1 to 6 carbon atoms. Examples include: alkyl group of 1 to 6 carbon atoms such as e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or hexyl.

Alkenyl means a branched or unbranched hydrocarbon radical of 2 to 6 carbon atoms containing at least one carbon-carbon double bond, each double bond being independently cis, trans or nongeometric isomer.

Alkynyl means a branched or unbranched hydrocarbon radical having 2 to 6 carbon atoms containing at least one carbon-carbon triple bond

Perfluoroalkyl means an alkyl group which includes both straight chain as well as branched moieties of 2 to 6 carbon atoms wherein each hydrogen has been replaced by a fluorine atom. An example is trifluoromethyl.

Alkyl, alkenyl, alkynyl and cycloalkyl groups may be unsubstituted (carbons bonded to hydrogen, or other carbons in the chain or ring) or may be mono- or poly-substituted.

Halogen means bromine, chlorine, fluorine, and iodine.

Cycloalkyl denotes a 3 to 6 membered ring such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Suitable substituents of aryl, heteroaryl, alkyl, alkenyl, alkynyl, and cycloalkyl include, but are not limited to hydrogen, halogen, alkyl of 1 to 6 carbon atoms; alkenyl of 2 to 6 carbon atoms; alkynyl of 2 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, $-OR_8$, -CN, $-COR_8$, perfluoroalkyl of 1 to 4 carbon atoms, -O-perfluoroalkyl of 1 to 4 carbon atoms, $-CONR_{13}R_{14}$, $-S(O)_nR_{13}$, $-OPO(OR_{13})OR_{14}$, $-PO(OR_{13})R_{14}$, $-OC(O)NR_{13}R_{14}$, $-C(O)NR_{13}OR_{14}$, $-COOR_{13}$, $-SO_3H$, $-NR_{13}R_{14}$, $-N[(CH_2)_2]_2NR_{13}$, $-NR_{13}COR_{14}$, $-NR_{13}COOR_{14}$, $-SO_2NR_{13}R_{14}$, $-NO_2$, $-N(R_{13})SO_2R_{14}$, $-NR_{13}CONR_{13}R_{14}$, $-NR_{13}C(=NR_{14})NR_{13}R_{14}$, $-NR_{13}C(=NR_{14})N(SO_2R_{13})R_{14}$, $NR_{13}C(=NR_{14})N(C=OR_{13})R_{14}$ -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_{13}R_{14}$, phenyl, heteroaryl, or - cycloheteroalkyl;

wherein $-NR_{13}R_{14}$ may form a pyrrolidine, piperidine, morpholine, thiomorpholine, oxazolidine, thiazolidine, pyrazolidine, piperazine, or azetidine ring; and when a moiety contains more than substituent with the same designation (i.e., phenyl tri-substituted with R_1) each of those substituents (R_1 in this case) may be the same or different; and R_8, R_{13} and R_{14} are as hereinabove defined.

Accordingly examples of alkyl groups for each independently of R_{1-7}, include C_1-C_6 alkyl which may be optionally substituted by one or more, e.g. three, substituents the same or different selected from halogen, alkyl of 1 to 6 carbon atoms; $-OR_8$, -CN, $-COR_8$, $-CONR_{13}R_{14}$, $-S(O)_nR_{13}$, $-OPO(OR_{13})OR_{14}$, $-PO(OR_{13})R_{14}$, $-OC(O)NR_{13}R_{14}$, $-C(O)NR_{13}OR_{14}$, $-COOR_{13}$, $-SO_3H$, $-NR_{13}R_{14}$, $-N[(CH_2)_2]_2NR_{13}$, $-NR_{13}COR_{14}$, $-NR_{13}COOR_{14}$, $-SO_2NR_{13}R_{14}$, $-NO_2$, $-N(R_{13})SO_2R_{14}$, $-NR_{13}CONR_{13}R_{14}$, $-NR_{13}C(=NR_{14})NR_{13}R_{14}$, $-NR_{13}C(=NR_{14})N(SO_2R_{13})R_{14}$, $NR_{13}C(=NR_{14})N(C=OR_{13})R_{14}$ -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_{13}R_{14}$,

phenyl, phenyl substituted by one to five substituents heteroaryl, or -cycloheteroalkyl;
wherein -$NR_{13}R_{14}$ may form a pyrrolidine, piperidine, morpholine, thiomorpholine, oxazolidine, thiazolidine, pyrazolidine, piperazine, or azetidine ring.

Similarly examples of aryl or heteroaryl groups for each independently of A, Y and R_1, R_2, $R_{6\text{-}11}$ include aryl or heteroaryl which may be optionally substituted by one or more, e.g. three, substituents the same or different selected from halogen, alkyl of 1 to 6 carbon atoms; -OR_8, -CN, -COR_8, -$CONR_{13}R_{14}$, -$S(O)_nR_{13}$, -$OPO(OR_{13})OR_{14}$, -$PO(OR_{13})R_{14}$, -$OC(O)NR_{13}R_{14}$, -$C(O)NR_{13}OR_{14}$, -$COOR_{13}$, -SO_3H, -$NR_{13}R_{14}$, -$N[(CH_2)_2]_2NR_{13}$, -$NR_{13}COR_{14}$, -$NR_{13}COOR_{14}$, -$SO_2NR_{13}R_{14}$, -NO_2, -$N(R_{13})SO_2R_{14}$, -$NR_{13}CONR_{13}R_{14}$, -$NR_{13}C(=NR_{14})NR_{13}R_{14}$, -$NR_{13}C(=NR_{14})N(SO_2R_{13})R_{14}$, $NR_{13}C(=NR_{14})N(C=OR_{13})R_{14}$ -tetrazol-5-yl, -SO_2NHCN, -$SO_2NHCONR_{13}R_{14}$, phenyl, phenyl substituted by one to five substituents heteroaryl, or cycloheteroalkyl; wherein -$NR_{13}R_{14}$ may form a pyrrolidine, piperidine, morpholine, thiomorpholine, oxazolidine, thiazolidine, pyrazolidine, piperazine, or azetidine ring.

Alkali metal base as used herein means an alkali metal hydroxide, preferably, sodium hydroxide, potassium hydroxide and lithium hydroxide.

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids when a compound of this invention contains a basic moiety. Salts may also be formed from organic and inorganic bases, preferably alkali metal salts, for example, sodium, lithium, or potassium, when a compound of this invention contains an acidic moiety.

The compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically

pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof. It is recognized that one optical isomer, including diastereomer and enantiomer, or stereoisomer may have favorable properties over the other. Thus when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

The compounds of this invention are shown to inhibit the enzymes MMP-1, MMP-9, MMP-13 and TNF-α converting enzyme (TACE) and are therefore useful in the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, graft rejection, insulin resistance, bone disease and HIV infection. In particular, the compounds of the invention provide enhanced levels of inhibition of the activity of TACE *in vitro* and in cellular assay and/or enhanced selectivity over MMP-1 and are thus particularly useful in the treatment of diseases mediated by TNF.

In particular, a therapeutically effective amount of a compound of Formula (I) of this invention is useful as a method of treating a pathological condition mediated by TNF-α converting enzyme (TACE) in mammals and useful in the treatment of rheumatoid arthritis, osteoarthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease, degenerative cartilage loss, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV.

Further, a therapeutically effective amount of a compound of Formula (I) of this invention is useful as a method of treating a pathological condition mediated by matrix metalloproteinases in mammals and useful in the treatment of rheumatoid arthritis, osteoarthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease, degenerative cartilage loss, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV.

The present invention accordingly provides a pharmaceutical composition which comprises a compound of this invention in combination or association with a

pharmaceutically acceptable carrier. In particular, the present invention provides a pharmaceutical composition which comprises an effective amount of compound of this invention and a pharmaceutically acceptable carrier.

The compositions are preferably adapted for oral administration. However, they may be adapted for other modes of administration, for example, parenteral administration for patients.

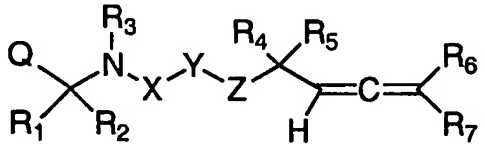
In order to obtain consistency of administration, it is preferred that a composition of the invention is in the form of a unit dose. Suitable unit dose forms include tablets, capsules, and powders in sachets or vials. Such unit dose forms may contain from 0.1 to 100 mg of a compound of the invention. The compounds of the present invention can be administered orally at a dose range of about 0.01 to 100 mg per kg. Such composition may be administered from 1 to 6 times a day, more usually from 1 to 4 times a day.

The compositions of the invention may be formulated with conventional excipients, such as fillers, a disintegrating agent, a binder, a lubricant, a flavoring agent, and the like. They are formulated in conventional manner.

The invention also provides a process for making compounds of the formula (I)

which process comprises:

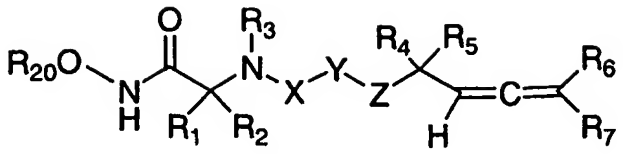
a) reacting a compound of formula V:



(V)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, X, Y and Z are as defined herein and Q is COOH or a reactive derivative thereof, with hydroxylamine to give a corresponding compound of formula (I); or

b) deprotecting a compound of formula VI:



(VI)

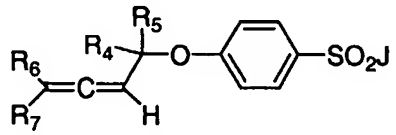
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, X, Y and Z are as defined herein, and R_{20} is a protecting group, to give a compound of formula (I);

c) resolving a mixture (e.g racemate) of optically active isomers of a compound of formula (I) to isolate one enantiomer or diastereomer substantially free of the other enantiomer or diastereomers;

or

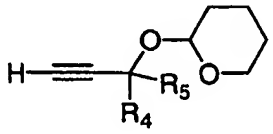
d) acidifying a basic compound of formula (I) with a pharmaceutically acceptable acid to give a pharmaceutically acceptable salt.

The invention is further directed to a process for preparing intermediate compounds of the formula



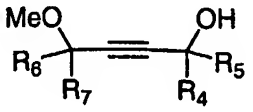
useful for preparing compounds of Formula (I) comprising the steps:

(a) reacting an alkynyl reagent of the formula :



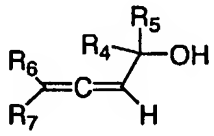
wherein R_4 and R_5 are as hereinabove defined, with a carbonyl compound of the formula:

wherein R_6 and R_7 are as hereinabove defined, in the presence of a strong base such as n-BuLi, in the presence of methyl iodide (MeI), and an organic acid such as preferably pyridinium p-toluenesulfonic acid to produce an alcohol of the formula :



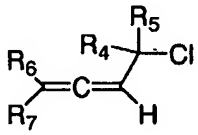
wherein R_4, R_5, R_6, and R_7 are as hereinabove defined;

(b) reacting an alcohol of step a above with a hydride reagent such as lithium aluminum hydride (LAH) and in the presence of iodine to produce an allene of the formula :



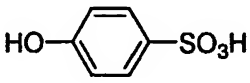
wherein R_4, R_5, R_6, and R_7 are as hereinabove defined;

(c) reacting an allene of step b with triphenylphosphine and triphosgene to produce a chloroallene of the formula :

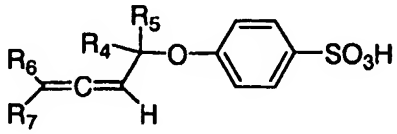


wherein R_4, R_5, R_6, and R_7 are as hereinabove defined;

(d) reacting a chloroallene of step c with a sulfonic acid of the formula, or a salt or solvate thereof:

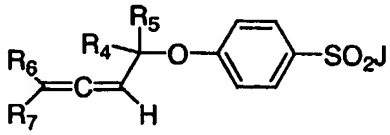


in the presence of an alkali metal base such as preferably sodium hydroxide to produce an ether of formula :



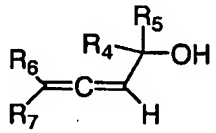
wherein R_4, R_5, R_6, and R_7 are as hereinabove defined;

(e) reacting an ether of step d, or a salt or a solvate thereof, with a chlorinating agent such as thionyl chloride, chlorosulfonic acid, oxalyl chloride, or phosphorous pentachloride, or other halogenating agents such as fluorosulfonic acid or thionyl bromide to produce an allene of the formula :



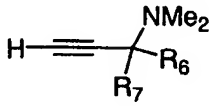
wherein R_4, R_5, R_6, and R_7 are as hereinabove defined, and J is F, Cl, or Br.

The invention is further directed to a process for preparing an allene of the formula :



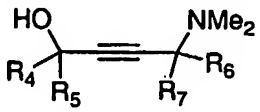
useful for the synthesis of compounds of Formula I, which comprises the steps of

(a) reacting an amine of the formula:



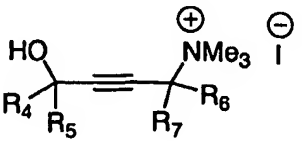
wherein R_6 and R_7 are as hereinabove defined, with a carbonyl compound of the formula:

wherein R_4 and R_5 are as hereinabove defined, in the presence of a strong base such as preferably n-butyllithium, to produce an alcohol of the formula :



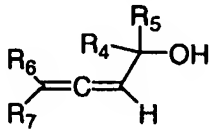
wherein R_4, R_5, R_6, and R_7 are as hereinabove defined;

(b) reacting an alcohol of step a, with methyl iodide to produce an alcohol of the formula:

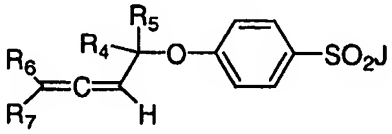


wherein R_4, R_5, R_6, and R_7 are as hereinabove defined;

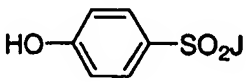
(c) reacting an alcohol of step b, with a hydride reducing agent such as preferably lithium aluminum hydride to produce an allene of the formula :



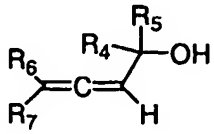
The invention is further directed to a process for preparing an allene of the formula:



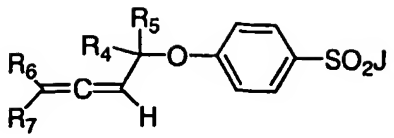
useful for making compounds of Formula I, wherein R_4, R_5, R_6, and R_7 are as hereinabove defined and J is F, Cl, or Br, by reacting a phenol of the formula :



wherein J is as hereinabove defined, with an alcohol of the formula,



in the presence of triphenyl phosphine, and diethylazodicarboxylate to produce an allene of the formula



Compounds of the present invention are conveniently prepared using conventional techniques known to those skilled in the art. The starting materials used in preparing the compounds of the invention are known, made by known methods as described in the following references or are commercially available. U. S. Patent. No. 5,753,653; Kogami, Yuji; Okawa, Kenji. *Bull. Chem. Soc. Jpn.* 1987, *60*(8), 2963; Auvin, S.; Cochet, O.; Kucharczyk, N.; Le Goffic, F.; Badet, B. *Bioorganic Chemistry*, 1991, *19*, 143; Angle, S. R.; Breitenbucher, J. G.; Arnaiz, D. O. *J. Org. Chem.* 1992, *57*, 5947; Asher, Vikram; Becu, Christian; Anteunis, Marc J. O.; Callens, Roland *Tetrahedron Lett.* 1981, *22*(2), 141; Levin, J. I.; DiJoseph, J. F.; Killar, L. M.; Sung, A.; Walter, T.; Sharr, M. A.; Roth, C. E.; Skotnicki, J. S.; Albright, J. D. *Bioorg. & Med. Chem. Lett.* 1998, *8*, 2657; U. S. Patent 5,770,624; Pikul, S.; McDow Dunham, K. L.; Almstead, N. G.; De, B.; Natchus, M. G.; Anastasio, M. V.; McPhail, S. J.; Snider, C. E.; Taiwo, Y. O.; Rydel, T.; Dunaway, C. M.; Gu, F.; Mieling, G. E. *J. Med. Chem.* 1998, *41*, 3568; U. S. Patent. Nos. 5,455,258, 5,506,242, 5,552,419 and 5,770,624; MacPherson, *et. al.* in *J. Med. Chem.*, 1997, *40*, 2525; U. S. Patent. Nos. 5,455,258 and 5,552,419; U. S. Patent. No. 5,804,593; Tamura, *et. al.* in *J. Med. Chem.* 1998, *41*, 640.

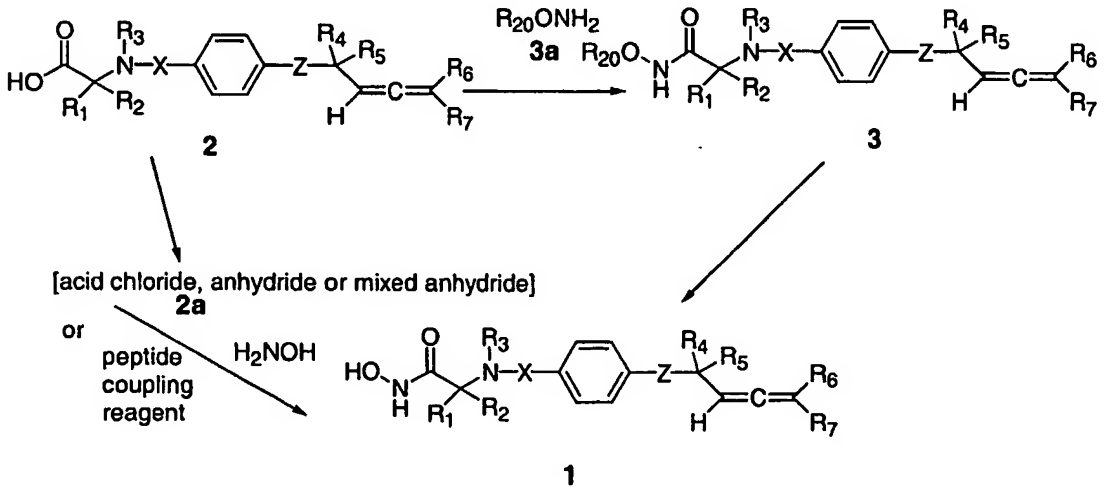
Those skilled in the art will recognize that certain reactions are best carried out when other potentially reactive functionality on the molecule is masked or protected, thus avoiding undesirable side reactions and/or increasing the yield of the reaction. To this end, those skilled in the art may use protecting groups. Examples of these protecting group moieties may be found in T. W. Greene, P. G. M. Wuts "Protective Groups in Organic Synthesis", 2nd Edition, 1991, Wiley & Sons, New York. Reactive side chain functionalities on amino acid starting materials are preferably protected. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (hydroxy, amino, carboxy, etc.), the structure and stability of the molecule of which the substituent is part and the reaction conditions. In particular, chapter 2 describes

protection/deprotection of hydroxyl groups, chapter 5 describes protection/deprotection of carboxyl groups and chapter 7 describes protection/deprotection of amino groups.

When preparing or elaborating compounds of the invention containing heterocyclic rings, those skilled in the art recognize that substituents on that ring may be prepared before, after or concomitant with construction of the ring. For clarity, substituents on such rings have been omitted from the schemes herein below.

Those skilled in the art will recognize that the nature and order of the synthetic steps presented may be varied for the purpose of optimizing the formation of the compounds of the invention.

Scheme 1



According to Scheme 1, hydroxamic acids **1**, of the invention are prepared by converting a carboxylic acid **2**, to the corresponding acid chloride, anhydride or mixed anhydride **2a** followed by reaction with hydroxylamine. Alternatively, rather than forming the acid chloride, anhydride or mixed anhydride, reacting carboxylic acid **2** directly with a suitable peptide coupling reagent which include for example, but not limited to N,N'-Dicyclohexylcarbodiimide plus 1-hydroxybenzotriazole; Benzotriazol-1-yloxytris (dimethylamino)phosphonium hexafluorophosphate (BOP-reagent); N,N'-Bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (BOB- Cl); Diphenylphosphinyl chloride (DPP-Cl); Diethoxyphosphoryl cyanide; 2-Chloro-1-methylpyridinium iodide; or Phenyldichlorophosphate plus imidazole followed by

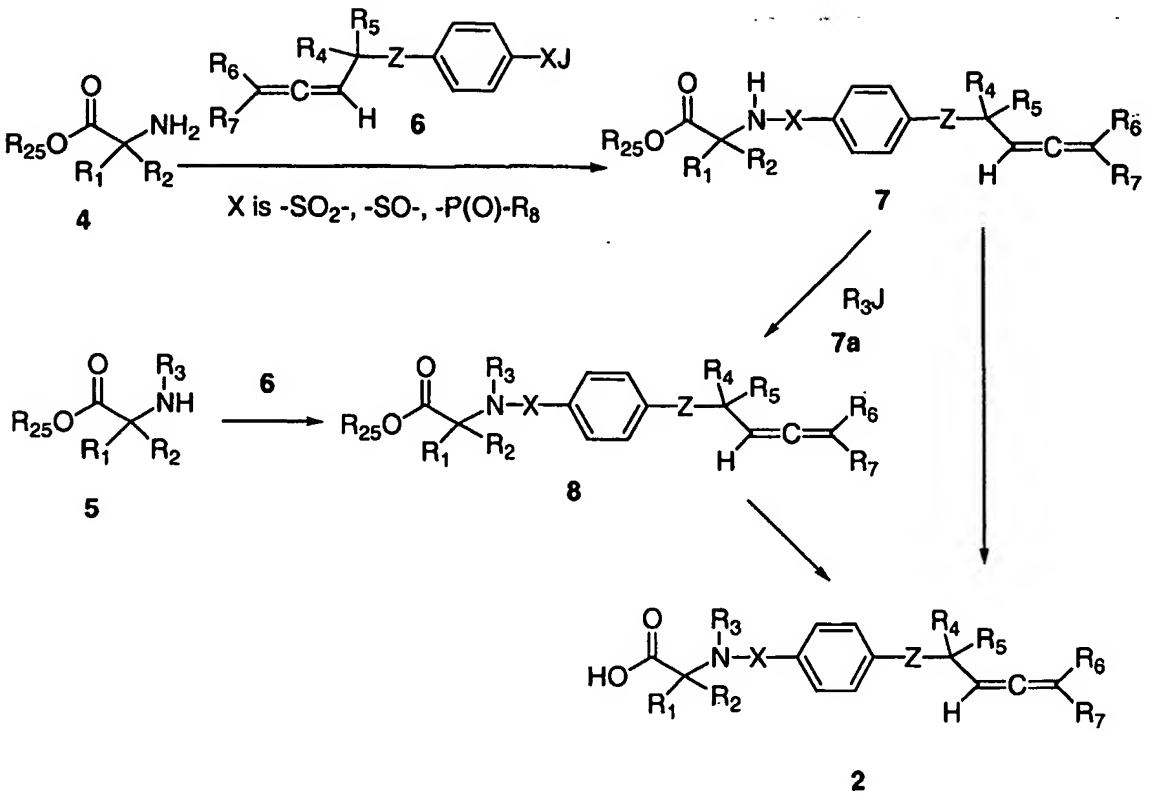
reaction with hydroxylamine also gives hydroxamic acids **1**. Acid chlorides, anhydrides, mixed anhydrides or peptide coupling reagent products **2a** are defined as activating agents. Further, reaction of carboxylic acid **2** with a protected hydroxylamine derivative **3a** gives allene **3**. Allene **3**, wherein R_{20} is a t-butyl, benzyl, tri-alkylsilyl or other suitable masking group, may then be deprotected by known methods which includes treatment with acid to provide the hydroxamic acid **1**.

Activating agents **2a** are formed by reaction of carboxylic acid **2** with activating reagents which include:

A chlorinating agent such as thionyl chloride, chlorosulfonic acid, oxalyl chloride, or phosphorous pentachloride, or other halogenating agents such as fluorosulfonic acid or thionyl bromide, suitable peptide coupling reagents which include for example, but not limited to N,N'-Dicyclohexylcarbodiimide plus 1-hydroxybenzotriazole; Benzotriazol-1-yloxytris (dimethylamino)phosphonium hexafluorophosphate (BOP-reagent); N,N'-Bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (BOB- Cl); Diphenylphosphinyl chloride (DPP-Cl); Diethoxyphosphoryl cyanide; 2-Chloro-1-methylpyridinium iodide; or Phenyldichlorophosphate plus imidazole; or preparation of a mixed anhydride with ethyl chloroformate.

Carboxylic acids **2** may be prepared as shown in Scheme 2. Amino acid derivative **4**, in which R_{25} is hydrogen or a suitable carboxylic acid protecting group, may be sulfonylated or phosphorylated by reacting with allene **6**, where J is a suitable leaving group including, but not limited to chlorine. The amino acid derivative **7** may then be alkylated with R_3J **7a** and a base such as potassium carbonate or sodium hydride in a polar aprotic solvent such as acetone, N,N-dimethylformamide (DMF), or tetrahydrofuran (THF) to provide protected acid **8**. Protected acid **8** is also available through direct reaction of allene **6** with an N-substituted amino acid derivative **5**. Conversion of the amino acid derivative **7** or protected acid **8** into the carboxylic acid **2** is performed by acid or base hydrolysis, or other method consistent with the choice of protecting group R_{25} and the presence of an allenic functionality.

Scheme 2

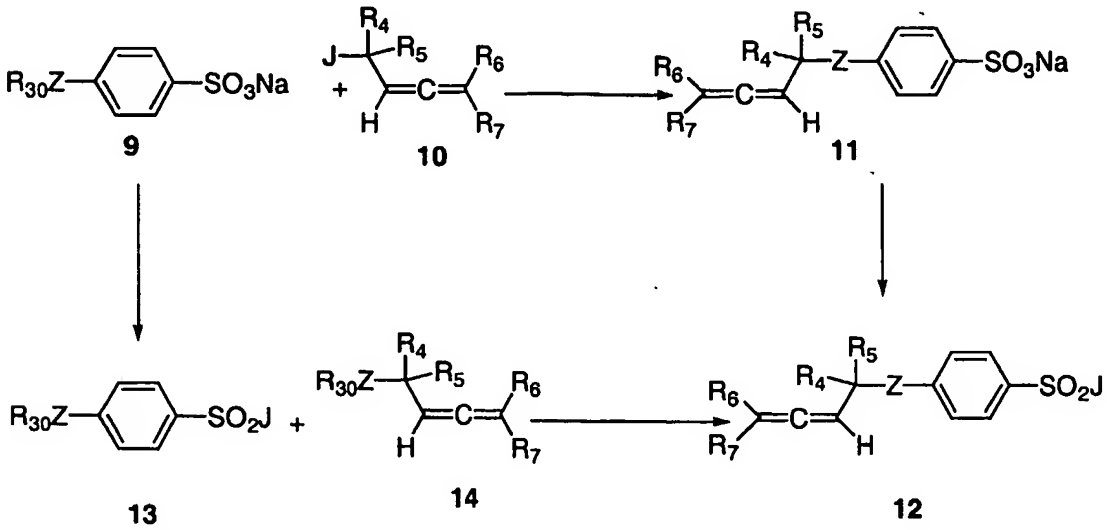


A method of preparation of sulfonyl chloride **12** is shown in Scheme 3. The sulfonic acid salt **9**, where ZR_{30} is a hydroxyl, thiol, or substituted amine moiety may be reacted with allenes **10**, where J is a suitable leaving group such as halogen, mesylate, tosylate, or triflate (Lathbury, D.; Gallagher, T. *J. Chem. Soc. Chem. Comm.* 1986, 114.: Black, D. K.; Landor, S.R.; Patel, A.N.; Whiter, P.F. *J. Chem. Soc. (C)* 1967, 2260.) to give sulfonic acid salt **11**. The sulfonic acid salt **11** can be converted into the corresponding sulfonyl chloride **12** by known methods such as reaction with oxalyl chloride or other reagent compatible with the allenic functionality.

Alternatively, the sulfonic acid salt **9** can be converted into the corresponding sulfonyl chloride, or other sulfonylating agent **13** (Campbell, R.W.; Hill, H.W. *J. Org. Chem.* 1973, *38*, 1047.), where ZR_{30} is a hydroxyl group, which can then be treated with an allenic alcohol **14** (Cowie, J.S.; Landor, P.D.; Landor, S.R. *J. Chem. Soc. Perkin I* 1973, 720.: Galanty, E.; Bacso, I.; Coombs, R.V. *Synthesis* 1974, 344: Keck,

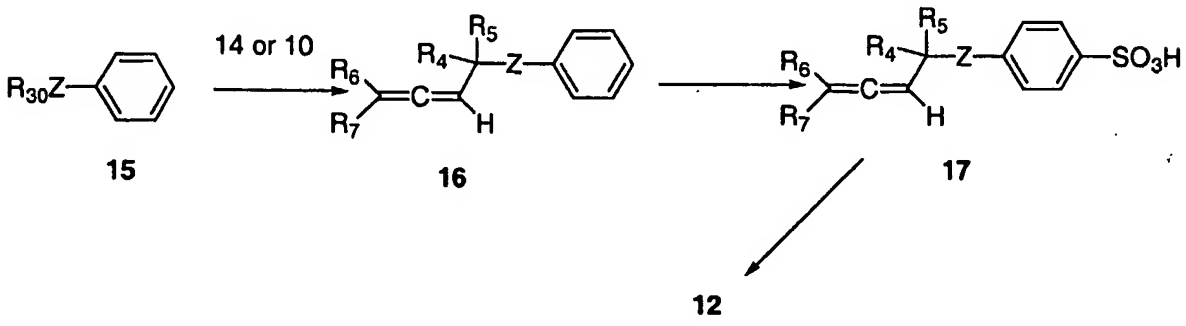
G.E.; Webb, R.R. *Tetrahedron Lett.* 1982, *23*, 3051), where ZR_{30} is a hydroxyl moiety, under Mitsunobu conditions to give sulfonyl chloride **12**.

Scheme 3



Further, as shown in Scheme 4, phenol or thiophenol **15** where Z is O or S respectively, may be alkylated with allene **10** or allene **14** under basic conditions or Mitsunobu conditions respectively, to give **16**, followed by reaction with chlorosulfonic acid to provide sulfonic acid **17**. Sulfonic acid **17** can be readily converted to sulfonyl chloride **12** with oxalyl chloride or other suitable reagent.

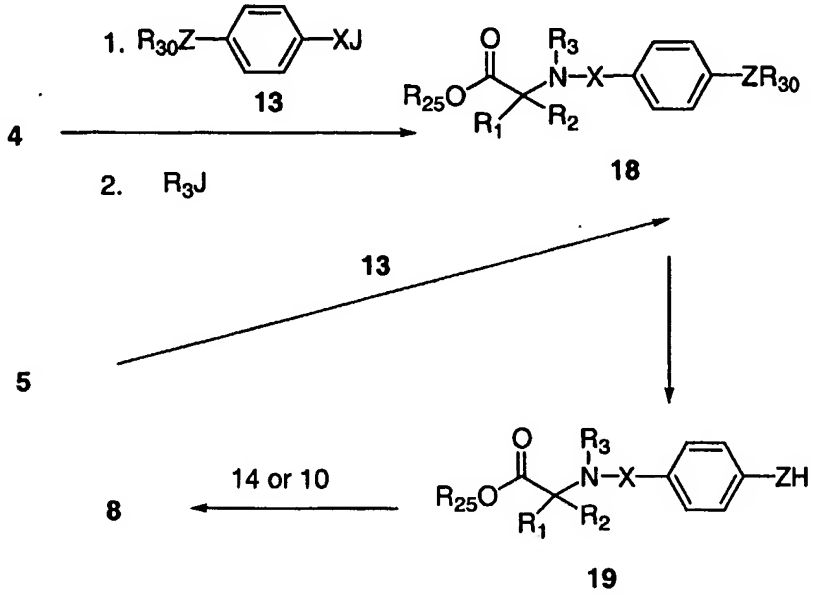
Scheme 4



The allenic side chain of amino acid derivative 4 or N-substituted amino acid derivative **5** may be appended as shown in the Scheme 5. Thus, the amino acid derivative **4** or N-substituted amino acid derivative **5** may be sulfonylated with phenol or protected phenol **13**, followed by alkylation with R_3J where ZR_{30} is hydroxyl or

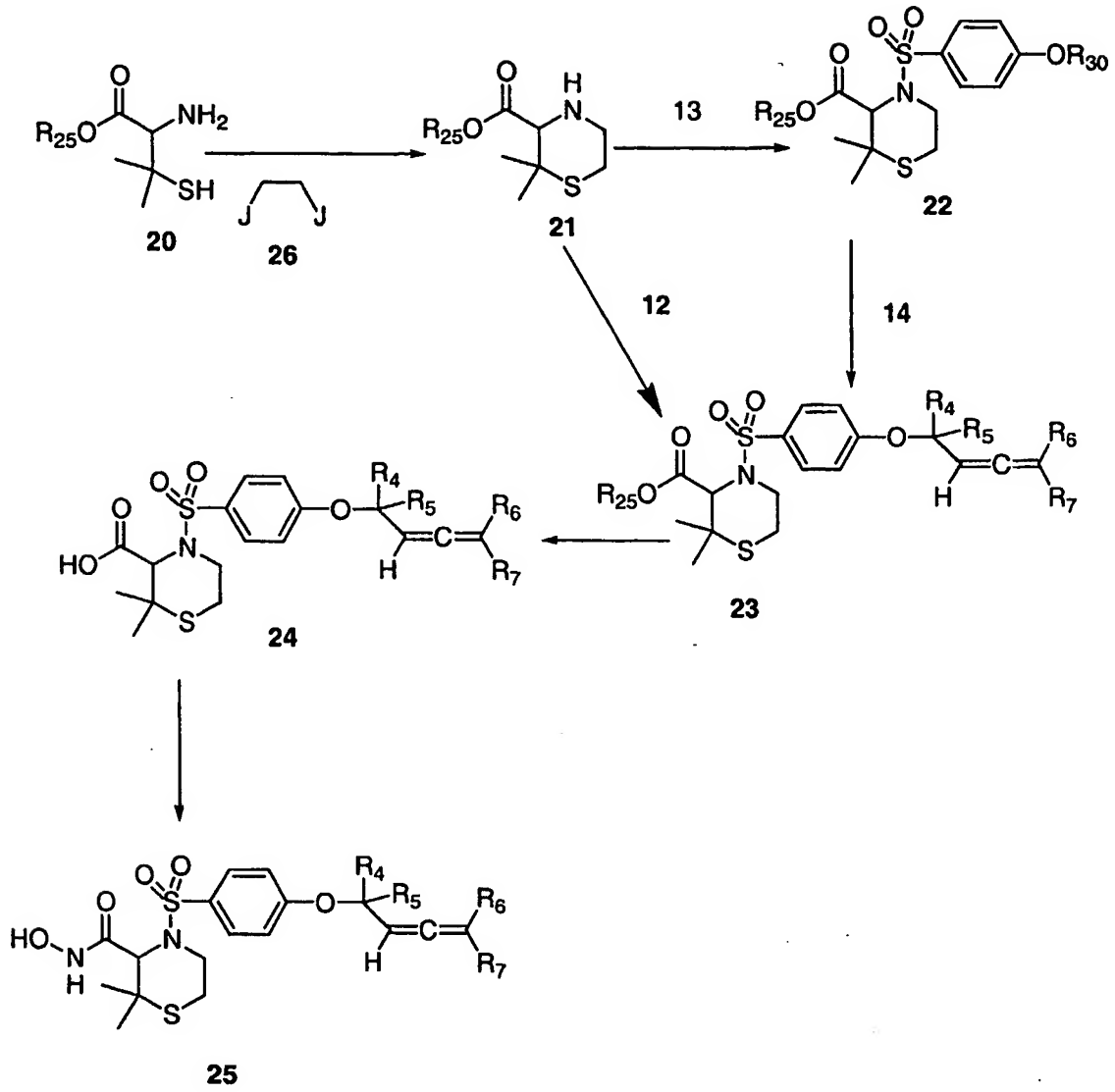
protected hydroxyl group and X is hereinbefore defined to give protected acid **18**. Removal of the protecting group R_{30} provides protected acid **19**, which can be alkylated with either allene **10** or **14** to provide protected acid **8**.

Scheme 5



Compounds of the invention in which R_1 and R_3 together form a thiomorpholine ring may be made according to the Scheme 6. Thiol **20** may be alkylated with disubstituted alkyl **26**, where J is a suitable leaving group, under basic conditions to give thiomorpholine **21**. Thiomorpholine **21** may be directly sulfonylated with sulfonyl chloride **12** to give sulfone **23**, or it can first be sulfonylated with **13** where Z is -O- and X is $-SO_2-$ and J is Cl to give thiomorpholine **22** followed by reaction with allene **14** to give sulfone **23** under Mitsunobu conditions. Sulfone **23** may be converted into carboxylic acid **24** by removal of the glocking group R_{25} followed by reaction with hydroxyl amine according to the methods described in Schemes 1 and 2 to afford hydroxamic acid **25**.

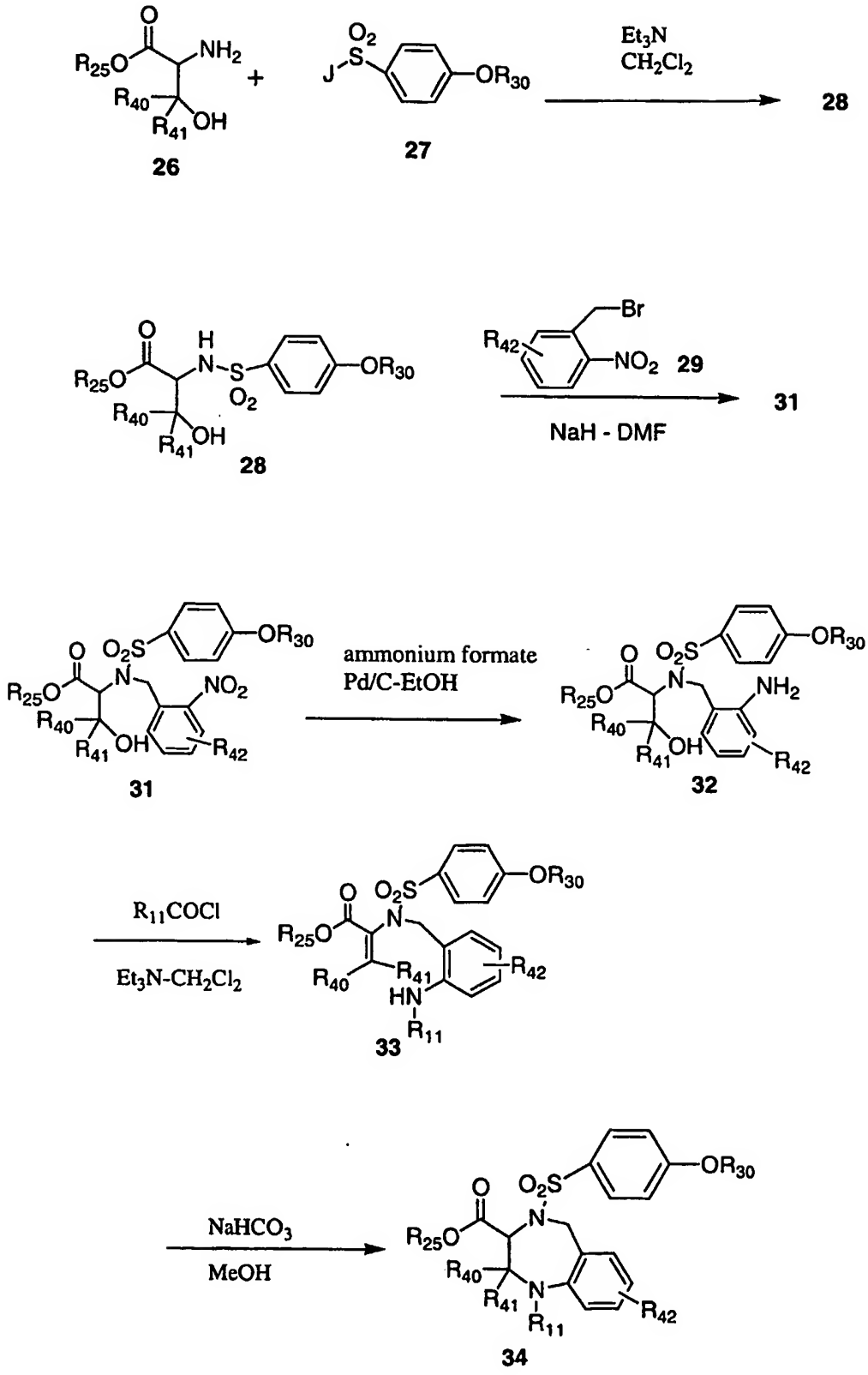
Scheme 6



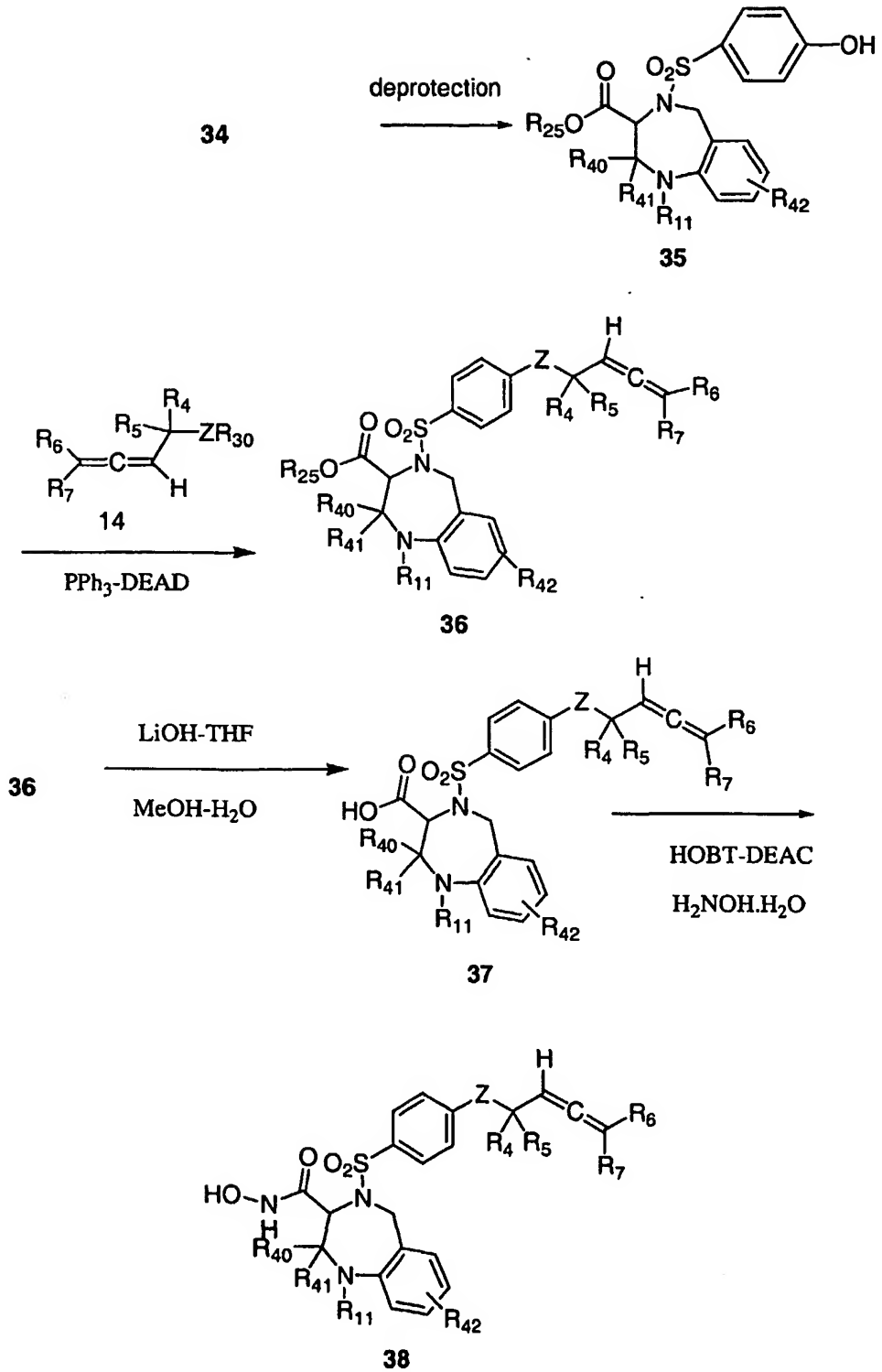
Compounds of the invention in which R_1 and R_3 taken together form a benzodiazepine ring can be made according to the Scheme 7 (WO200044730). Protected amino acids **26** wherein R_{40} and R_{41} are each H or methyl such as threonine, serine, β-hydroxyvaline, and related derivatives can be converted into the corresponding sulfonamide **28** by reacting with benzenesulfonyl halide **27** in the presence of a base such as triethylamine. The sulfonamide **28** can be alkylated with suitable substituted or unsubstituted 2-nitrobenzyl halides **29** under conditions such

as sodium hydride in N,N-dimethylformamide (DMF)to provide the corresponding nitro derivative **31**. Reduction under conventional reducing conditions such as catalytic hydrogenation(with Pd/C) or chemical reduction (with $SnCl_2$ or $FeCl_3$) provides N-(2-aminobenzyl)derivative derivative **32**. Reaction of N-(2-aminobenzyl)derivative **32** with various acid chlorides and sulfonyl chlorides, in the presence of trialkyl amines or pyridine, provides the dehydro derivative **33**. Ring closure of the dehydro derivative **33** to the [1,4]benzodiazepine derivative **34** is carried out by reacting with a mild base such as sodium or potassium bicarbonate in an alcohol solvent such as methanol or ethanol. Deprotecting the blocking group R_{30} of [1,4]benzodiazepine derivative **34** , provides phenol **35**. Phenol **35** can be alkylated with the allenic alcohol **14** under Mitsunobu conditions as shown in the Schemes 4, 5, and 6 to afford ester derivative **36** which can be converted to sulfone **37** in the presence of lithium hydroxide. Hydroxamic acid derivative **38** is prepared following conditions which include reaction of sulfone **37** with 1-hydroxybenzo-triazole(HOBT) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide(DEAC) followed by reaction with hydroxylamine or alternatively conditions as shown in the Scheme 1 and 2.

Scheme 7


Et3N
CH2Cl2
26
27
28
29
31
NaH - DMF
ammonium formate
Pd/C-EtOH
32
R11COCl
Et3N-CH2Cl2
33
NaHCO3
MeOH
34

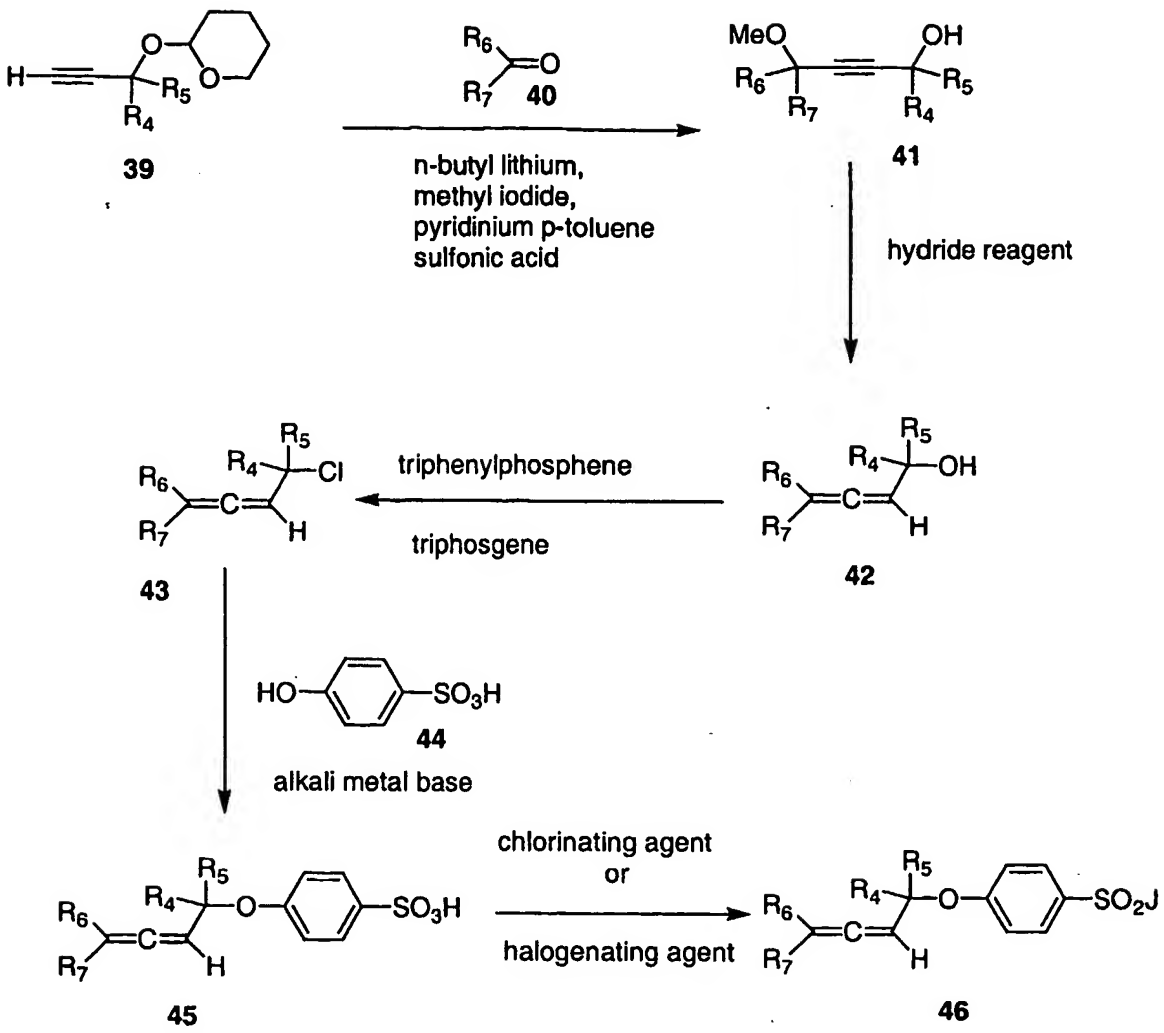
Scheme 7 (Cont'd)



The preparation of intermediate compounds useful in the preparation of compounds of Formula I are outlined in Schemes 8-10.

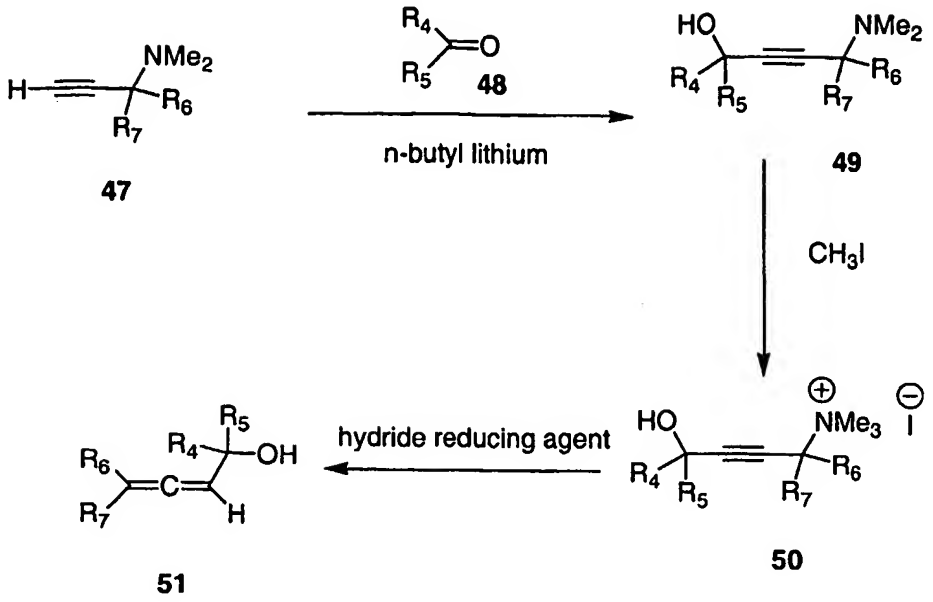
As shown in Scheme 8, alkynyl reagent **39** where R_4 and R_5 are hereinbefore defined is reacted with a carbonyl compound **40** where R_6 and R_7 are hereinbefore defined in the presence of a strong base, preferably butyl lithium, in a solvent such as tetrahydrofuran (THF) and the like in the presence of methyl iodide and and organic acid, preferably pyridinium p-toluenesulfonic acid to give alcohol **41** which is reduced with a hydride reagent, preferably lithium aluminum hydride (LAH) and iodine in a solvent such as tetrahydrofuran and the like to produce an allene **42.** Further reaction of allene **42** with triphenylphosphine and triphosgene in a chlorinated hydrocarbon solvent such as methylene chloride and the like affords chloro allene **43** which is further reacted with sulfonic acid **44** in the presence of an alkali metal base, preferably sodium hydroxide to give an ether **45** which is reacted with a chlorinating agent such as thionyl chloride, chlorosulfonic acid, oxalyl chloride, or phosphorous pentachloride or halogenating agent such as fluorosulfonic acid or thionyl bromide in solvents such as acetonitrile and sulfolane to afford allene **46**.

Scheme 8



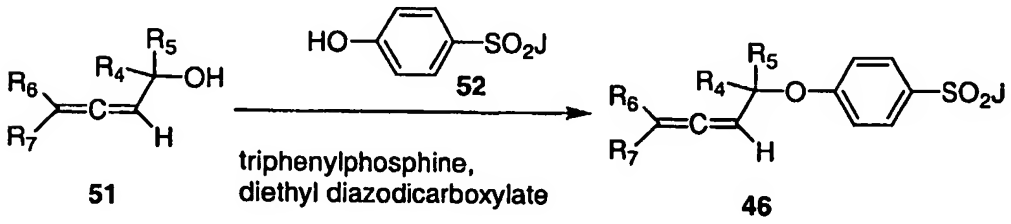
As shown further in Scheme 9, amine **47** where R_6 and R_7 are hereinbefore defined is reacted with carbonyl compound **48** where R4 and R5 are hereinbefore defined in the presence of a strong base, preferably butyl lithium in solvents such as tetrahydrofuran and the like to afford alcohol **49** which is further reacted with methyl iodide to give alcohol **50** which is reduced with a hydride reducing agent, preferably lithium aluminum hydride in solvents such as tetrahydrofuran and the like to give alcohol **51**.

Scheme 9



As described in Scheme 10, alcohol **51** is reacted with triphenylphosphine in the presence of diethyl diazodicarboxylate and phenol **52** in solvents such as benzene and the like to afford allene **46**.

Scheme 10



Pharmacology

Standard Pharmacological Test Procedures

Representative compounds of this invention were evaluated as inhibitors of the enzymes MMP-1, MMP-9, MMP-13 and TNF-a converting enzyme (TACE). The standard pharmacological test procedures used, and results obtained which establish this biological profile are shown below.

Test Procedures for Measuring MMP-1, MMP-9, and MMP-13 Inhibition

These standard pharmacological test procedures are based on the cleavage of a thiopeptide substrates such as Ac-Pro-Leu-Gly(2-mercapto-4-methyl-pentanoyl)-Leu-Gly-OEt by the matrix metalloproteinases MMP-1, MMP-13 (collagenases) or MMP-9 (gelatinase), which results in the release of a substrate product that reacts colorimetrically with DTNB (5,5'-dithiobis(2-nitro-benzoic acid)). The enzyme activity is measured by the rate of the color increase. The thiopeptide substrate is made up fresh as a 20 mM stock in 100% DMSO and the DTNB is dissolved in 100% DMSO as a 100 mM stock and stored in the dark at room temperature. Both the substrate and DTNB are diluted together to 1 mM with substrate buffer (50 mM HEPES pH 7.5, 5 mM $CaCl_2$) before use. The stock of enzyme is diluted with buffer (50 mM HEPES, pH 7.5, 5 mM $CaCl_2$, 0.02% Brij) to the desired final concentration. The buffer, enzyme, vehicle or inhibitor, and DTNB/substrate are added in this order to a 96 well plate (total reaction volume of 200 μl) and the increase in color is monitored spectrophotometrically for 5 minutes at 405 nm on a plate reader and the increase in color over time is plotted as a linear line.

Alternatively, a fluorescent peptide substrate is used. In this test procedure, the peptide substrate contains a fluorescent group and a quenching group. Upon cleavage of the substrate by an MMP, the fluorescence that is generated is quantitated on the fluorescence plate reader. The assay is run in HCBC assay buffer (50mM HEPES, pH 7.0, 5 mM Ca^{+2}, 0.02% Brij, 0.5% Cysteine), with human recombinant MMP-1, MMP-9, or MMP-13. The substrate is dissolved in methanol and stored frozen in 1 mM aliquots. For the assay, substrate and enzymes are diluted in HCBC buffer to the desired concentrations. Compounds are added to the 96 well plate containing enzyme and the reaction is started by the addition of substrate. The reaction is read (excitation 340 nm, emission 444 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line.

For either the thiopeptide or fluorescent peptide test procedures, the slope of the line is calculated and represents the reaction rate. The linearity of the reaction rate is confirmed (r^2 >0.85). The mean (x±sem) of the control rate is calculated and compared for statistical significance ($p<0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generated using

multiple doses of drug and IC_{50} values with 95% CI are estimated using linear regression.

Test Procedure for Measuring TACE Inhibition

Using 96-well black microtiter plates, each well receives a solution composed of 10 μL TACE (final concentration 1μg/mL), 70μL Tris buffer, pH 7.4 containing 10% glycerol (final concentration 10 mM), and 10 μL of test compound solution in DMSO (final concentration 1μM, DMSO concentration <1%) and incubated for 10 minutes at room temperature. The reaction is initiated by addition of a fluorescent peptidyl substrate (final concentration 100 μM) to each well and then shaking on a shaker for 5 sec.

The reaction is read (excitation 340 nm, emission 420 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line. The slope of the line is calculated and represents the reaction rate.

The linearity of the reaction rate is confirmed (r^2 >0.85). The mean (x±sem) of the control rate is calculated and compared for statistical significance ($p<0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generate using multiple doses of drug and IC_{50} values with 95% CI are estimated using linear regression.

Results of the above *in vitro* matrix metalloproteinase inhibition and TACE inhibition following these these standard pharmacological test procedures are give In Table 1 below.

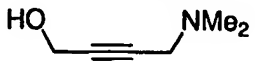
TABLE 1

	IC50 (nM)			
Ex. No.	MMP-1	MMP-9	MMP-13	TACE
13	2668	36	21	51
16	138	3	3	36
19	8806	21	25	62
22	877	4	6	48
26	50	-	4	116
45	2353	9	7	71
46	675	-	4	515
47	32%(1μM	-	5	1400

The present invention will now be illustrated with reference to the following, non-limiting examples.

Example 1

4-But-2-ynyloxybenzenesulfonyl fluoride

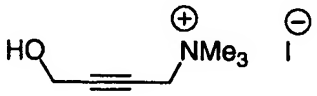


To a solution of 1-dimethyl-2-aminopropyne (10g, 120 mmol) in tetrahydrofuran (270 ml) at -78°C was added n-butyllithium (52.8 mL, 132 mmol) and the resulting mixture was stirred for 20 minutes. A suspension of formaldehyde (3.96g, 132 mmol) in tetrahydrofuran (150 ml) was then added and the mixture was stirred at -78°C for 1 hour. The reaction was allowed to warm to room temperature, quenched with a saturated ammonium chloride solution and extracted with ethyl acetate. The removal of the solvent *in vacuo* gave 10g (74%) of the product.

^{1}H NMR(300 MHz, $CDCl_3$):δ 2.30 (s, 6H), 3.26 (m, 2H), 4.26 (m, 2H).

Example 2

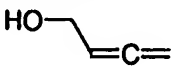
1-(tert-Butyl) 4-methyl 1,4-piperidinecarboxylate



To a solution of product from Example 1 (8g, 70.8 mmol) in acetone (300 ml) was added methyl iodide (15g, 105.6 mmol) and the resulting mixture was stirred for 4 hours at room temperature. The solid was collected and dried to give 13.5g (75%) of the salt.

Example 3

Buta-2,3-diene-1-ol



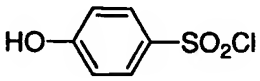
To a suspension of product from Example 2 (10g, 39.2 mmol) in tetrahydrofuran (200 ml) was added lithium aluminium hydride (2.23g, 58.7 mmol) and the resulting mixture was stirred for 4 hours. The mixture was quenched with

Rochelle's salt and extracted with diethyl ether. The organic layer was washed with 1N hydrochloric acid, saturated sodium thiosulfate solution, saturated sodium chloride and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give 2.15g (98%) of the product as an oil.

^{1}H NMR(300 MHz, $CDCl_3$):δ 1.73 (m, 1H), 4.15 (m, 2H), 4.86 (m, 2H), 5.36 (m, 1H); ^{13}C NMR(75 MHz, $CDCl_3$):δ 60.6, 77.5, 91.2, 208.0.

Example 4

1-(tert-Butoxycarbonyl)-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-4–piperidinecarboxylic acid

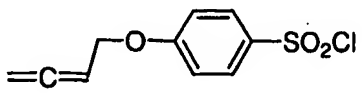


A solution of thionyl chloride (16 ml, 200 mmol) and dimethylformamide (0.3 ml) was quickly added to solid sodium 4-hydroxybenzenesulfonate (10g, 40 mmol) in a flask and the resulting mixture was heated at 60°C for 3 hours. The mixture was poured into ice with vigorous stirring, methylene chloride was added and aqueous layer was separated. The aqueous layer was extracted with additional methylene chloride and the organic layers were washed with ice-water and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give 4g (52%) of the product as a solid.

^{1}H NMR(300 MHz, DMSO-d_6):δ 5.36 (brs, 1H), 6.98 (d, 2H, J= 9.0 Hz), 7.96 (d, 2H, J= 9.0 Hz).

Example 5

4-(2,3-Butadienyloxy)benzenesulfonyl chloride



To a solution of product from Example 4 (1.98g, 10.28 mmol) in benzene (70 ml) was added product from Example 3 (600 mg, 8.57 mmol) followed by diethylazodicarboxylate (1.6 ml, 10.28 mmol). A solution of triphenylphosphine (2.7g, 10.28 mmol) in benzene (10 ml) was added, dropwise, to the reaction mixture and the resulting solution was stirred for 15 minutes at room temperature. The solid

formed was collected and removal of the solvent *in vauo* gave the crude product, which was purified by flash chromatography to give 850mg (41%) of the product.
IR: 1956, 1590, 1576, 1372, 1260, 1166, 832 cm^{-1};
^1H NMR(300 MHz, $CDCl_3$): δ 4.68 (m, 2H), 4.93 (m, 2H), 5.38 (m, 1H), 7.04 (d, 2H, J= 9.0 Hz), 7.98(d, 2H, J= 9.0 Hz);
^{13}C NMR(75 MHz, $CDCl_3$): δ 66.9, 77.6, 86.3, 115.8, 129.8, 136.5, 164.0, 210.0.

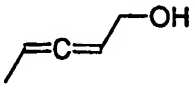
Example 6

4-(Methoxy)penta-2-ynyl-1-ol

To a solution of n-butyllithium (64 ml, 156.8 mmol) in tetrahydrofuran (300 ml) at -78°C was added a solution of tetrahydro-2-(2-propynyloxy)-2H-pyran (20g, 142.6 mmol) in tetrahydrofuran (100 ml), dropwise, and the mixture was stirred for 10 minutes. A solution of acetaldehyde (8 ml, 142.6 mmol) was then added and the resulting mixture was stirred for 20 minutes at -78°C. Neat methyl iodide (36 ml, 570 mmol) was added and the mixture was allowed to warm to room temperature. Hexamethyldiphosphorylamide (40 ml) was added while the reaction was warming to room temperature and the mixture was stirred for 1.5 hours. The reaction was quenched with water and extracted with diethyl ether. To a solution of the crude product in methanol (200 ml) was added pyridinium p-toluenesulfonate (1.5g). The mixture was stirred overnight, neutralized with a saturated sodium bicarbonate solution, and the solventl was removed *in vacuo*. The crude product was partitioned between water and ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the residue was distilled (95°C at 20 mmHg) to give 12g (75%) of the product as a liquid.
IR: 3416, 2936, 1449, 1112, 850 cm^{-1};
^1H NMR(300 MHz, $CDCl_3$):δ 1.43 (d, 3H, J= 6.6 Hz), 1.79 (brs, 1H), 3.40 (s, 3H), 4.11 (m, 1H), 4.32 (m, 2H);
^{13}C NMR(75 MHz, $CDCl_3$): δ 22.2, 51.4, 56.7, 67.2, 83.6, 85.7;
MS(ES): m/z 115 $(M+H)^+$.

Example 7

Penta-2,3-dien-1-ol



To a solution of product from Example 6 (430mg, 3.77 mmol) in diethyl ether (30 ml) was added, in portions, lithium aluminum hydride (287mg, 7.54 mmol) at room temperature and the mixture was stirred for 10 minutes. Solid iodine was added in one batch to the cooled (-78°C) solution and the resulting mixture was stirred for 2 hours. The -78°C bath was replaced with an ice-bath and a saturated solution of Rochelle's salt was added, dropwise, until distinct layers are formed. The excess iodine was removed by addition of a sodium thiosulfate solution. The diethyl ether layer was separated, dried over anhydrous sodium sulfate and removal of the solvent *in vacuo* gave 350mg (91%) of the product.

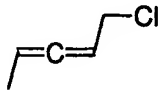
IR: 3379, 2936, 1967, 1725, 1374, 1080, 877 cm^{-1};

^1H NMR(300 MHz, $CDCl_3$):δ 1.69 (m, 3H), 2.27 (brs, 1H), 4.14 (m, 2H), 5.26 (m, 2H);

^{13}C NMR(75 MHz, $CDCl_3$):δ 14.5, 61.0, 88.6, 91.4, 205.0.

Example 8

1-Chloro-penta-2,3-diene



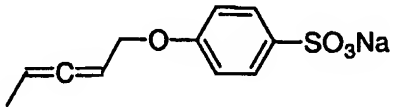
To a solution of triphenylphosphene (1.36g, 5.2 mmol) in methylene chloride (25 ml) was added, in portions, triphenylphosgene (593mg, 2.0 mmol) and the resulting mixture was stirred for 5 minutes at room temperature. A solution of product from Example 7 (400mg, 4.76 mmol) was added and the mixture was stirred for 30 minutes.

The reaction mixture was distilled *in vacuo*, collection the distillate in a –78°C trap. The distillate was redistilled (b.p. 56°C at 100 mmHg) to give 200mg (41%) of the product as a liquid.

^1H NMR(300 MHz, $CDCl_3$):δ 1.69 (m, 3H), 4.05 (m, 2H), 5.27 (m, 2H).

Example 9

4-(2,3-Pentadienyloxy)benzenesulfonic acid sodium salt



To a suspension of sodium 4-hydroxybenzenesulfonate (1.3g, 5.6 mmol) in iso-propanol (20 ml) was added product from Example 8 (700mg, 6.8 mmol) followed by 1N sodium hydroxide (6.1 ml, 6.1 mmol) and the resulting mixture was heated at 65-70°C for 15 hours. The reaction mixture was concentrated *in vacuo*, the solid collected and washed with diethy ether to give 880mg (53%) of the product as a solid.

IR: 1973, 1182, 1139, 1051, 834 cm^{-1};

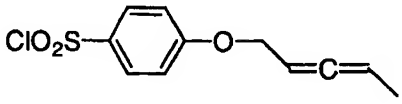
^1H NMR(300 MHz, D_2O):δ 1.46 (m, 3H), 4.53 (m, 2H), 5.22 (m, 2H), 6.95 (d, 2H, J= 9.0 Hz), 7.64 (d, 2H, J= 9.0 Hz);

^{13}C NMR(75 MHz, D_2O):δ 13.3, 66.5, 86.5, 88.9, 115.6, 127.9, 135.5, 160.1, 206.1;

HR – MS: m/z Calculated for $C_{11}H_{12}O_4S$(M - H): 239.0383; Found 239.0386.

Example 10

4-(2,3-Pentadienyloxy)benzenesulfonyl chloride



To a suspension of product from Example 9 (740mg, 2.48 mmol) in acetonitrile (2 ml) and sulfolane (2 ml) was added phosphoryl chloride (0.9 ml, 9.93 mmol) and the resulting mixture was heated at 60-65°C for 2 hours. The mixture was cooled in ice and cold water was added, dropwise, while stirring was continued for an additional 15 minutes. The reaction mixture was extracted with ethyl acetate and the organic layer was dried over anhydrous sodium sulfate. The crude residue was purified by flash chomatography to give 415mg (65%) of the product.

IR: 2928, 1970, 1590, 1576, 1166, 1085, 833 cm^{-1};

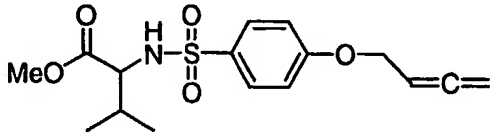
^{1}H NMR(300 MHz, $CDCl_3$):δ 1.74 (m, 3H), 4.66 (m, 2H), 5.29 (m, 2H), 7.06 (d, 2H, J= 9.0 Hz), 7.99 (d, 2H, J= 9.0 Hz);

^{13}C NMR(75 MHz, $CDCl_3$):δ 14.1, 67.4, 86.2, 88.7, 115.9, 129.8, 136.4, 164.1, 208.0;

MS – ES:m/z 258$(M+H)^+$.

Example 11

Methyl 2-({[4-(2,3-butadienyloxy)phenyl]sulfonyl}amino)-3-methylbutanoate



To a solution of DL-valine methyl ester hydrochloride (527 mg, 3.15 mmol) was added triethylamine (579 mg, 5.72 mmol) followed by product from Example 5 (700 mg, 2.86 mmol) and the resulting mixture was stirred for 10 hours at room temperature. The solvent was removed *in vacuo* and the residue was partitioned between water and ethyl acetate. The organic layer was washed with 1N hydrochloric acid, saturated sodium bicarbonate, saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave 850 mg (87%) of the product as a solid.

IR: 3283, 2969, 1962, 1737, 1595, 1259, 839 cm^{-1};

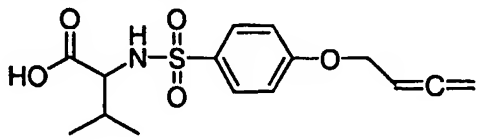
^{1}H NMR(300 MHz, $CDCl_3$): δ 0.87 (d, 3H, J= 6.9 Hz), 0.95 (d, 3H, J= 6.9 Hz), 2.02 (m, 2H), 3.47 (s, 3H), 3.71 (m, 1H), 4.62 (m, 2H), 4.90 (m, 2H), 5.02 (d, 1H, J= 10.2 Hz), 5.36 (m, 1H), 6.96 (d, 2H, J= 9.0 Hz), 7.75 (d, 2H, J= 9.0 Hz);

^{13}C NMR(75 MHz, $CDCl_3$): δ 17.4, 18.9, 31.6, 52.2, 61.0, 66.1, 77.2, 86.3, 115.0, 129.4, 131.4, 161.8, 171.9, 209.7;

HR – MS: m/z Calculated for $C_{16}H_{21}NO_5S$: 340.1213; Found 340.1221.

Example 12

N-{[4-(2,3-Butadienyloxy)phenyl]sulfonyl}valine



To a solution of product from Example 11 (300 mg, 0.88 mmol) in a mixture of tetrahydrofuran (5 ml), methanol (5 ml), and water (3 ml) was added lithium hydroxide (64 mg, 2.67 mmol) and the resulting mixture was heated at 60°C for 8 hours. The mixture was concentrated *in vacuo* followed by the addition of water. The solution was acidified to pH ~2 with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and the solvent was removed to give 250 mg (81%) of the product.

IR: 3266, 2967, 1961, 1723, 1594, 1332, 1163, 829 cm^{-1};

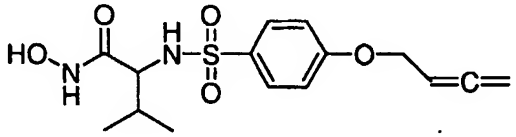
^1H NMR(300 MHz, DMSO-d_6): δ 0.78 (d, 3H, J= 6.3 Hz), 0.81 (d, 3H, J= 6.3 Hz), 1.92 (m, 1H), 3.31 (s, 3H), 3.44 (m, 1H), 4.63 (m, 2H), 4.98 (m, 2H), 5.51 (m, 1H), 7.06 (d, 2H, J= 9.0 Hz), 7.69 (d, 2H, J= 9.0 Hz), 7.82 (d, 1H, J= 9.3 Hz), 12.51 (s, 1H);

^{13}C NMR(75 MHz, DMSO-d_6): δ 17.7, 18.9, 30.2, 61.0, 65.3, 77.0, 86.3, 114.6, 128.6, 133.0, 160.6, 172.1, 208.7;

HR – MS: m/z Calculated for $C_{15}H_{19}NO_5S$: 326.1057; Found 326.1052.

Example 13

2-({[4-(2,3-Butadienyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-methylbutanamide



To a solution of product from Example 12 (210 mg, 0.65 mmol) in dimethylformamide (6 ml) was added 1-hydroxybenzotriazol (105 mg, 0.78 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodimide hydrochloride (173 mg, 0.90 mmol), and N-methylmorpholine (0.106 mmol, 0.97 mmol) and the resulting mixture was stirred for 1 hour at room temperature. A 50% aqueous solution of hydroxylamine (0.119 ml, 1.94 mmol) was added and the mixture was stirred for 15 hours at room temperature. The reaction mixture was concentrated *in vacuo*, diluted with water, and extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, water, saturated sodium bicarbonate, saturated sodium chloride and dried over

anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave 100 mg(45%) of the product.

IR: 3313, 2973, 1954, 1671, 1594, 1324, 1253, 1153, 829 cm^{-1};

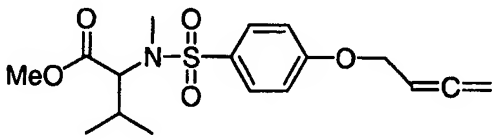
^1H NMR(300 MHz, DMSO-d_6): δ 0.72 (t, 6H, J= 7.2 Hz), 1.75 (m, 1H), 3.25 (m, 1H), 4.64 (m, 2H), 4.98 (m, 2H), 5.51 (m, 1H), 7.06 (d, 2H, J= 9.0 Hz), 7.67 (d, 2H, J= 9.0 Hz), 7.75 (d, 1H, J= 9.3 Hz), 8.78 (d, 1H, J= 1.8 Hz), 10.48 9d, 1H, J= 1.8 Hz);

^{13}C NMR(75 MHz, DMSO-d_6): δ 18.8, 19.2, 31.0, 59.9, 65.7, 77.5, 84.2, 86.8, 115.0, 128.8, 133.8, 160.9, 167.1, 209.2;

HR – MS: m/z Calculated for $C_{15}H_{20}N_2O_5S$: 341.1166; Found 341.1163.

Example 14

Methyl 2-[{[4-(2,3-butadienyloxy)phenyl]sulfonyl}(methyl)amino]-3-methylbutanoate



A solution of product from Example 11 (400 mg, 1.18 mmol) in tetrahydrofuran (10 ml) was added to a suspension of 60% sodium hydride (57 mg, 1.42 mmol) in tetrahydrofuran (2 ml) and the resulting mixture was stirred for 30 minutes, at which time methyl iodide (335 mg, 2.36 mmol) was added. The resulting mixture was stirred for 15 hours and partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the crude residue was purified by flash chromatography to give 350 mg (84%) of the product.

IR: 2971, 1958, 1735, 1593, 13336, 1255, 1144, 993 cm^{-1};

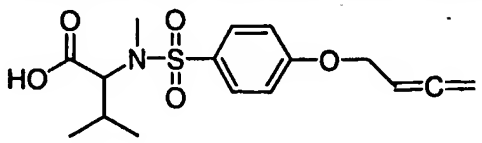
^1H NMR(300 MHz, $CDCl_3$): δ 0.92 (d, 3H, J= 6.6 Hz), 0.98 (d, 3H, J= 6.6 Hz), 2.07 (m, 1H), 2.86 (s, 3H), 3.43 (s, 3H), 4.11(d, 1H, J= 10.8 Hz), 4.62 (m, 2H), 4.89 (m, 2H), 5.37 (m, 1H), 6.96 (d, 2H, J= 9.0 Hz), 7.72 (d, 2H, J= 9.0 Hz);

^{13}C NMR(75 MHz, $CDCl_3$): δ 19.1, 27.8, 29.9, 51.3, 64.6, 66.1, 77.2, 86.3, 114.7, 129.4, 130.9, 161.5, 170.7, 209.7;

HR – MS: m/z Calculated for $C_{17}H_{23}NO_5S$: 354.1370; Found 354.1378.

Example 15

N-{[4-(2,3-Butadienyloxy)phenyl]sulfonyl}valine



The procedure of Example 12 was followed using the product from Example 14 (300 mg, 0.85 mmol) and lithium hydroxide (41 mg, 1.7 mmol) in tetrahydrofuran (3 ml), methanol (3 ml), and water (1.5 ml) to give 247 mg (86%) of the product.

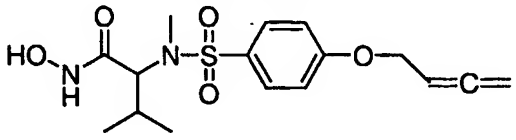
IR: 2970, 1956, 1707, 1592, 1334, 1154, 835 cm^{-1};

^1H NMR(300 MHz, DMSO-d_6): δ 0.82 (d, 3H, J= 6.6 Hz), 0.89 (d, 3H, J= 6.6 Hz), 1.95 (m, 1H), 2.76 (s, 3H), 3.88 (d, 1H, J= 10.5 Hz), 4.64 (m, 2H), 5.00 (m, 2H), 5.51 (m, 1H), 7.08 (d, 2H, J= 9.0 Hz), 7.69 (d, 2H, J= 9.0 Hz);

HR – MS: m/z Calculated for $C_{16}H_{21}NO_5S$: 340.1213; Found 340.1204.

Example 16

2-[{[4-(2,3-Butadienyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxy-3-methylbutanamide



The procedure of Example 13 was followed using the product from Example 15 (250 mg, 0.74 mmol), 1-hydroxybenzotriazol (119 mg, 0.88 mmol), 1-[3-(dimethylamino)-propyl]-3-ethylcarbodimide hydrochloride (199 mg, 1.04 mmol), N-methylmorpholine (0.122 mmol, 1.11 mmol), and hydroxylamine (0.226 ml, 3.7 mmol) to give 150 mg (57%) of the product.

IR: 3351, 3238, 2969, 1957, 1653, 1594, 1327, 1150, 834 cm^{-1};

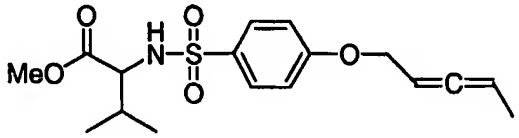
^1H NMR(300 MHz, DMSO-d_6): δ 0.78 (m, 6H), 2.02 (m, 1H), 2.80 (s, 3H), 3.70 (d, 1H, J= 10.8 Hz), 4.65 (m, 2H), 5.00 (m, 2H), 5.51 (m, 1H), 7.08 (d, 2H, J= 9.0 Hz), 7.69 (d, 2H, J= 9.0 Hz), 8.87 (s, 1H), 10.80 (s, 1H);

^{13}C NMR(75 MHz, DMSO-d_6): δ 19.1, 19.5, 27.1, 30.0, 62.0, 65.8, 77.5, 86.7, 115.3, 129.3, 131.3, 161.3, 165.7, 209.2;

HR – MS: m/z Calculated for $C_{16}H_{22}N_2O_5S$: 355.1322; Found 355.1313.

Example 17

Methyl 3-methyl-2-({[4-(2,3-pentadienyloxy)phenyl]sulfonyl}amino)butanoate



The procedure of Example 11 was followed using DL-valine methyl ester hydrochloride (246 mg, 1.47 mmol), the product from Example 10 (388.0 mg, 1.5 mmol), and triethylamine (297 mg, 2.94 mmol) in methylene chloride (10 ml) to give 350 mg (68%) of the product.

IR: 3261, 2967, 1968, 1732, 1595, 1159, 996, 834 cm^{-1};

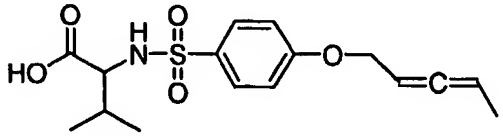
^1H NMR(300 MHz, $CDCl_3$): δ 0.87 (d, 3H, J= 6.9 Hz), 0.94 (d, 3H, J= 6.9 Hz), 1,67 (m, 3H), 2.02 (m, 1H), 3.46 (s, 3H), 3.71 (m, 1H), 4.59 (m, 2H), 5.26 (m, 3H), 6.97 (d, 2H, J= 9.0 Hz), 7.77 (d, 2H, J= 9.0 Hz);

^{13}C NMR(75 MHz, $CDCl_3$): δ 13.7, 17.5, 18.9, 31.5, 52.2, 61.0, 66.7, 86.2, 88.0, 114.9, 129.3, 131.2, 161.8, 171.8, 206.0;

HR – MS: m/z Calculated for $C_{17}H_{23}NO_5S$: 353.1298; Found 353.1297.

Example 18

N-{[4-(2,3-Pentadienyloxy)phenyl]sulfonyl}valine



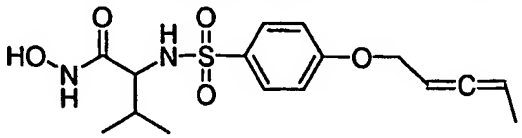
The procedure of Example 12 was followed using the product from Example 17 (320 mg, 0.91 mmol) and lithium hydroxide (64 mg, 2.67 mmol) in tetrahydrofuran (5 ml), methanol (5 ml), and water (3 ml) to give 250 mg (81%) of the product.

IR: 3279, 2969, 1972, 1715, 1595, 1160, 835 cm^{-1};

^{1}H NMR(300 MHz, acetone-d_6): δ 0.89 (d, 3H, J= 6.9 Hz), 0.95 (d, 3H, J= 6.9 Hz), 1.63 (m, 3H), 2.09 (m, 1H), 3.14 (brs, 1H), 3.68 (m, 1H), 4.65 (m, 2H), 5.32 (m, 2H), 6.43 (d, 1H, J= 9.2 Hz), 7.05 (d, 2H, J= 9.0 Hz), 7.78 (d, 2H, J= 9.0 Hz);
^{13}C NMR(75 MHz, acetone-d_6): δ 14.3, 18.2, 19.8, 32.3, 62.2, 67.5, 87.8, 88.7, 116.0, 130.4, 134.3, 162.8, 173.0, 206.0;
HR – MS: m/z Calculated for $C_{16}H_{21}NO_5S$: 339.1141; Found 339.1116.

Example 19

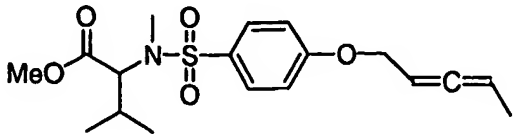
N-Hydroxy-3-methyl-2-({[4-(2,3-pentadienyloxy)phenyl]sulfonyl}amino)butanamide



The procedure of Example 13 was followed using the product from Example 18 (230 mg, 0.67 mmol), 1-hydroxybenzotriazol (80 mg, 0.59 mmol), 1-[3-(dimethylamino)-propyl]-3-ethylcarbodimide hydrochloride (132 mg, 0.69 mmol), N-methylmorpholine (0.81 mmol, 0.74 mmol), and hydroxylamine (0.150 ml, 2.45 mmol) in dimethylformamide (5 ml) to give 100 mg (42%) of the product.
IR: 3739, 3318, 2969, 1971, 1672, 1595, 1323, 1154, 998 cm^{-1};
^{1}H NMR(300 MHz, DMSO-d_6): δ 0.72 (m, 6H), 1.59 (m, 3H), 1.75 (m, 1H), 3.24 (t, 1H, J= 8.4 Hz), 4.60 (dd, 2H, J_1= 2.4 Hz, J_2= 6.3 Hz), 5.35 (m, 2H), 7.05 (d, 2H, J= 9.0 Hz), 7.68 (d, 2H, J= 9.0 Hz), 7.70 (m, 1H), 8.77 (s, 1H), 10.47 (s, 1H);
^{13}C NMR(75 MHz, DMSO-d_6): δ 13.4, 18.4, 18.8, 30.6, 59.5, 65.7, 86.6, 87.3, 114.6, 128.3, 133.3, 160.5, 166.7, 205.3.
HR – MS: m/z Calculated for $C_{16}H_{22}N_2O_5S$ (M + Na): 377.1141; Found 377.1141.

Example 20

Methyl 3-methyl-2-(methyl{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}amino)butanoate



The procedure of Example 14 was followed using the product from Example 17 (300 mg, 0.85 mmol), sodium hydride (41 mg, 1.02 mmol), and methyl iodide (241 mg, 1.7 mmol) in tetrahydrofuran (8 ml) to give 240 mg (77%) of the product.

IR: 2965, 1969, 1739, 1594, 1496, 1340, 1148, 834 cm^{-1};

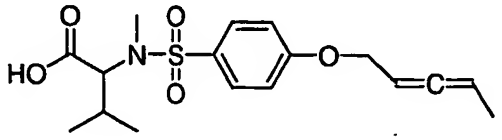
^1H NMR(300 MHz, $CDCl_3$): δ 0.92 (d, 3H, J= 6.6 Hz), 0.99 (d, 3H, J= 6.6 Hz), 1.68 (m, 3H), 2.08 (m, 1H), 2.85 (s, 3H), 3.43 (s, 3H), 4.13 (d, 1H, J= 6.9 Hz), 4.58 (m, 2H), 5.27 (m, 1H), 6.96 (d, 2H, J= 9.0 Hz), 7.71 (d, 2H, J= 9.0 Hz);

^{13}C NMR(75 MHz, $CDCl_3$): δ 13.7, 19.1, 19.2, 27.8, 29.9, 51.3, 64.6, 66.7, 67.3, 77.2, 86.3, 88.0, 114.8, 129.4, 130.7, 161.6, 170.7, 206.3;

HR – MS: m/z Calculated for $C_{18}H_{25}NO_5S$: 368.1526; Found 368.1533.

Example 21

N-Methyl-N-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}valine



The procedure of Example 12 was followed using the product from Example 20 (240 mg, 0.65 mmol), and lithium hydroxide (31 mg, 1.31 mmol) in tetrahydrofuran (2 ml), methanol (2 ml), and water (1 ml) to give 200 mg (87%) of the product.

IR: 3245, 2967, 1970, 1714, 1594, 1151, 833 cm^{-1};

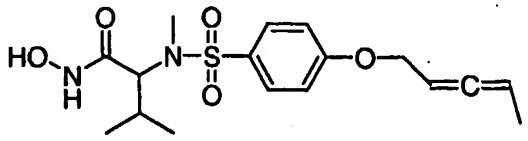
^1H NMR(300 MHz, DMSO-d_6): δ 0.82 (d, 3H, J= 6.6 Hz), 0.89 (d, 3H, J= 6.6 Hz), 1.59 (m, 3H), 2.75 (s, 3H), 3.88 (d, 1H, J= 10.5 Hz), 4.62 (m, 2H), 5.38 (m, 2H), 7.08 (d, 2H, J= 9.0 Hz), 7.68 (d, 2H, J= 9.0 Hz), 12.80 (brs, 1H);

^{13}C NMR(75 MHz, DMSO-d_6): δ 13.4, 18.9, 19.1, 27.0, 29.5, 64.4, 65.8, 86.5, 87.4, 114.9, 129.0, 130.4, 144.7, 161.0, 171.1, 205.4;

HR – MS: m/z Calculated for $C_{17}H_{23}NO_5S$: 354.1370; Found 354.1364.

Example 22

N-Hydroxy-3-methyl-2-(methyl{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}amino)butanamide



The procedure of Example 13 was followed using the product from Example 21 (185 mg, o.52 mmol), 1-hydroxybenzotriazol (84 mg, 0.62 mmol), 1-[3-(dimethylamino)-propyl]-3-ethylcarbodimide hydrochloride (140 mg, 0.73mmol), N-methylmorpholine (0.86 mmol, 0.78 mmol), and hydroxylamine (0.159 ml, 2.6 mmol) in dimethylformamide (5 ml) to give 120 mg (63%) of the product.

IR: 3357, 3223, 2918, 1970, 1653, 1596, 1327, 1150, 998 cm^{-1};

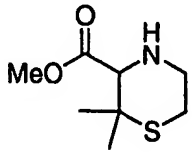
^1H NMR(300 MHz, DMSO-d_6): δ 0.78 (m, 6H), 1.60 (m, 3H), 2.02 (m, 1H), 2.79 (s, 3H), 3.71 (d, 1H, J= 10.8 Hz), 4.62 (m, 2H), 5.38 (m, 1H), 7.06 (d, 2H, J= 8.7 Hz), 7.69 (d, 2H, J= 8.7 Hz), 8.86 (s, 1H), 10.78 (s, 1H);

^{13}C NMR(75 MHz, DMSO-d_6): δ 13.4, 18.6, 19.1, 26.6, 29.5, 61.6, 65.8, 86.6, 87.4, 114.9, 128.8, 130.8, 160.9, 165.3, 205.4;

HR – MS: m/z Calculated for $C_{17}H_{24}N_2O_5S$: 369.1479; Found 369.1469.

Example 23

Methyl (3S)-2,2-dimethyl-3-thiomorpholinecarboxylate



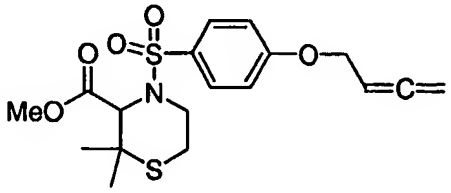
To a solution of 1,2-dibromoethane (6.77 g, 36 mmol) in dimethylformamide (25 ml) was added, over a period of 30 minutes, a solution of D-penicillamine methyl ester hydrochloride (6 g, 30 mmol) and 1,8-diazobicyclo[5.4.0]undeca-7-ene (13.7 g, 90 mmol) in dimethylformamide (50 ml). The resulting mixture was stirred for 18 hours at room temperature. The reaction mixture was poured into a saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was

dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to give 5.5 g (97%) of the product.

^{1}H NMR(300 MHz, $CDCl_3$):δ 1.29 (s, 3H), 1.42 (s, 3H), 1.78 (s, 1H), 2.29 (m, 1H), 2.94 (m, 3H), 3.39 (m, 1H), 3.72 (s, 3H).

Example 24

Methyl (3S)-4-{[4-(2,3-butadienyloxy)phenyl]sulfonyl}-2,2-dimethyl-3-thiomorpholinecarboxylate



To a solution of product from Example 23 (155 mg, 0.82 mmol) in methylene chloride (5 ml) was added N-methylmorpholine (0.180 ml, 1.64 mmol) followed by the product from Example 5 (200 mg, 0.82 mmol). The resulting mixture was stirred for 15 hours at room temperature. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate. The organic layer was washed with 1N hydrochloric acid, saturated sodium bicarbonate, saturated sodium chloride and dried over anhydrous sodium sulfate. The crude residue was purified by flash chromatography to give 170 mg(52%) of the product.

IR: 2960, 1957, 1745, 1594, 1495, 1156, 877 cm^{-1};

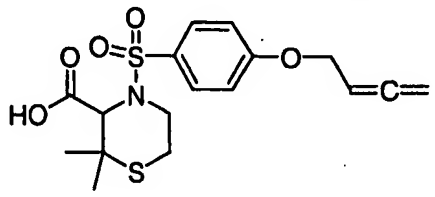
^{1}H NMR(300 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.61 (s, 3H), 2.46 (m, 1H), 3.12 (m, 1H), 3.41 (s, 3H), 3.76 (m, 1H), 4.05 (m, 1H), 4.41 (s, 1H), 4.62 (m, 2H), 4.89 (m, 2H), 5.36 (m, 1H), 6.94 (d, 2H, J= 9.0 Hz), 7.65 (d, 2H, J= 9.0 Hz);

^{13}C NMR(75 MHz, $CDCl_3$): δ 24.6, 27.2, 28.4, 29.7, 40.1, 41.2, 51.3, 62.7, 66.1, 86.3, 114.9, 129.1, 130.7, 161.7, 168.7, 209.6;

HR – MS: m/z Calculated for $C_{18}H_{23}NO_5S_2$: 398.1090; Found 398.1089.

Example 25

(3S)-4-{[4-(2,3-Butadienyloxy)phenyl]sulfonyl}-2,2-dimethyl-3-thiomorpholinecarboxylic acid



The procedure of Example 12 was followed using the product from Example 24 (150 mg, 0.38 mmol), lithium hydroxide (18 mg, 0.76 mmol) in tetrahydrofuran (2 ml), methanol (2 ml), and water (1 ml) to give 50 mg of product (53%, based on unreacted starting material).

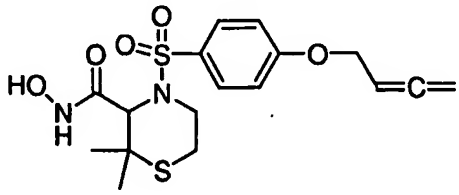
^{1}H NMR(300 MHz, acetone-d_6): δ 1.35 (s, 3H), 1.55 (s, 3H), 2.52 (m, 1H), 3.05 (m, 1H), 3.82 (m, 1H), 4.02 (m, 1H), 4.40 (s, 1H), 4.68 (m, 2H), 4.94 (m, 2H), 5.46 (m, 1H), 7.07 (d, 2H, J= 9.0 Hz), 7.75 (d, 2H, J= 9.0 Hz);

^{13}C NMR(75 MHz, acetone-d_6): δ 24.5, 27.3, 28.4, 40.0, 41.1, 62.7, 66.2, 77.2, 86.2, 115.0, 129.3, 130.7, 162.0, 172.3, 209.6;

HR – MS: m/z Calculated for $C_{17}H_{21}NO_5S_2$ 384.0933; Found 384.0932.

Example 26

(3S)-4-{[4-(2,3-Butadienyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide



The procedure of Example 13 was followed using the product from Example 25 (65 mg, 0.17 mmol), 1-hydroxybenzotriazol (28 mg, 0.20 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodimide hydrochloride (46 mg, 0.24 mmol), N-

methylmorpholine (0.028 ml, 0.26 mmol), and hydroxylamine (0.052 ml, 0.85 mmol) in dimethylformamide (1.5 ml) to give 40 mg (59%) of the product.

IR: 3351, 3241, 2963, 1960, 1655, 1594, 1153, 874 cm^{-1};

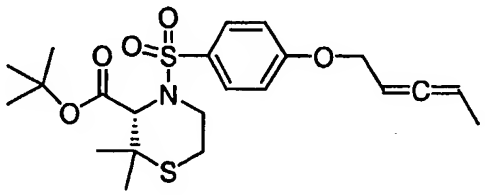
^1H NMR(300 MHz, DMSO-d_6): δ 1.22 (s, 3H), 1.46 (s, 3H), 2.61 (m, 1H), 2.93 (m, 1H), 3.80 (m, 1H), 4.02 (m, 1H), 4.09 (s, 1H), 4.72 (m, 2H), 5.07 (m, 2H), 5.58 (m, 1H), 7.13 (d, 2H, J= 9.0 Hz), 7.68 (d, 2H, J= 9.0 Hz), 8.91 (s, 1H), 10.8 (s, 1H);

^{13}C NMR(75 MHz, DMSO-d_6): δ 24.0, 26.5, 28.5, 41.0, 58.6, 65.4, 77.2, 86.4, 115.1, 128.7, 130.9, 161.1, 164.0, 208.9;

HR – MS: m/z Calculated for $C_{17}H_{22}N_2O_5S_2$: 399.1042; Found 399.1039.

Example 27

tert-Butyl (3S)-2,2-dimethyl-4-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-3-thiomorpholinecarboxylate



To a solution of tert-butyl 4-(4-hydroxybenzenesulfonyl)-2,2-dimethylthiomorpholine-3-carboxylate (697 mg, 1.8 mmol) in tetrahydrofuran (6 mL) was added triphenylphosphine (566 mg, 2.16 mmol) and the product from Example 7 (160 mg, 1.9 mmol) in tetrahydrofuran (4 mL) followed by diethylazodicarboxylate (0.312 mL, 1.98 mmol) at 0° C. The resulting mixture was stirred for 4 h at room temperature and the solvent was removed in vacuo. The residue was purified by silica gel column chromatagraphy to obtain the product (400 mg, 49%) as a white solid.

IR: 2975, 1969, 1736, 1594, 1154, 882 cm^{-1};

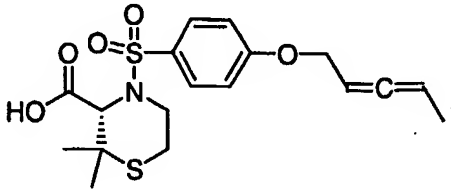
^1H NMR(400 MHz, $CDCl_3$): δ 1.30 (s, 9H), 1.32 (s, 3H), 1.61 (s, 3H), 1.68 (d, 3H, J= 7.2 Hz), 2.43 (m, 1H), 3.12 (m, 1H), 3.87 (m, 1H), 4.04 (m, 1H), 4.32 (s, 1H), 4.57 (m, 1H), 5.27 (m, 1H), 5.26 (m, 1H), 6.94 (d, 2H, J= 7.4 Hz), 7.66 (d, 2H, J= 7.4 Hz);

^{13}C NMR(100 MHz, $CDCl_3$): δ 13.7, 24.7, 27.6, 27.9, 28.7, 29.7, 40.3, 41.0, 63.1, 66.7, 82.1, 86.3, 88.0, 88.1, 115.1, 129.1, 131.5, 161.7, 167.6, 206.2, 206.3;

HR – MS: m/z Calculated for $C_{22}H_{31}NO_5S_2$: 454.1716; Found 454.1713.

Example 28

(3S)-2,2-dimethyl-4-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-3-thiomorpholinecarboxylic acid



To a solution of the product from Example 27 (200 mg, 0.44 mmol) in methylene chloride (4 mL) was added trifluoroacetic acid (1 mL) and the resulting mixture was stirred for 2 h at room temperature. The solvents were removed in vacuo and the residue was purified by silica gel column chromatagraphy to obtain the product (120 mg, 69%) as a white solid.

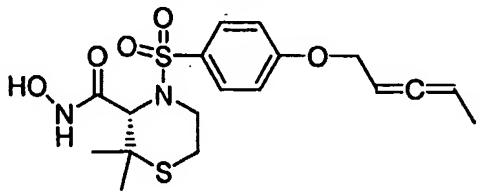
^{1}H NMR(400 MHz, acetone-d_6): δ 1.35 (s, 3H), 1.55 (s, 3H), 1.63 (m, 3H), 2.51 (m, 1H), 3.05 (m, 1H), 3.80 (m, 1H), 4.01 (m, 1H), 4.39 (s, 1H), 4.65 (m, 1H), 5.33 (m, 1H), 7.07 (d, 2H, J= 7.4 Hz), 7.71 (d, 2H, J= 7.4 Hz);

^{13}C NMR(100 MHz, acetone-d_6): δ 14.0, 15.6, 25.1, 27.9, 40.4, 41.9, 63.5, 66.1, 67.2, 87.4, 88.3, 115.8, 130.0, 162.7, 169.9, 206.1;

HR – MS: m/z Calculated for $C_{18}H_{23}NO_5S_2$ 415.1355; Found 415.1349.

Example 29

(3S)- N-Hydroxy-2,2-dimethyl-4-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-3-thiomorpholinecarboxamide



The procedure of Example 13 was followed using the product from Example 28 (190 mg, 0.46 mmol), 1-hydroxybenzotriazol (75 mg, 0.55 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodimide hydrochloride (123 mg, 0.64 mmol), N-

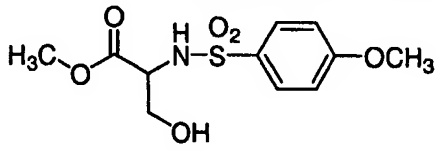
methylmorpholine (0.076 ml, 0.69 mmol), and hydroxylamine (0.141 ml, 2.3 mmol) in dimethylformamide (4 ml) to give 50 mg (32%) of the product.

^{1}H NMR(400 MHz, DMSO-d_6): δ 1.16 (s, 3H), 1.39 (s, 3H), 1.60 (m, 3H), 2.54 (m, 1H), 2.86 (m, 1H), 3.74 (m, 1H), 3.95 (m, 1H), 4.03 (s, 1H), 4.63 (m, 1H), 5.35 (m, 1H), 7.06 (d, 2H, J= 7.0 Hz), 7.62 (d, 2H, J= 7.0 Hz), 8.82 (s, 1H), 10.80 (s, 1H).

HR – MS: m/z Calculated for $C_{18}H_{24}N_2O_5S_2$: 413.1199; 413.1209.

Example 30

Methyl 3-Hydroxy-2-(4-methoxybenzenesulfonylamino)propionate



To a mixture of D,L-serine, methyl ester (5.0 g, 32.14 mmol) and triethylamine (15.7 ml, 0.012 mmol) in methylene chloride (100ml), cooled to 0°C, was added, in portions, 4-methoxybenzenesulfonyl chloride (6.64g, 32.14 mmol). The mixture was then stirred under argon at room temperature for 48 hours. The reaction was diluted with methylene chloride (100 ml), washed with water (60 ml), 2N citric acid (60 ml), saturated sodium chloride (60 ml), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give a solid. Crystallization from ethyl acetate gave 5.0 g (54%) of the product as white crystals, mp 92-94°C.

Analysis. for $C_{11}H_{15}NO_6S$:

Calc'd: C,45.7; H,5.2; N,4.8; S,11.1;

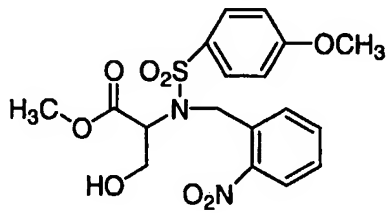
Found: C,45.6; H,5.2; N,4.8; S,11.1;

^{1}H NMR(300 MHz, $CDCl_3$): δ 2.04(b, 1H), 3.63(s, 3H), 3.87(s, 3H,), 3.89(d, 2H, J=3.7Hz), 3.97(m, 1H),5.66(d, 1H, J= 7.5 Hz); 6.98(d, 2H, J=9Hz); 7.8(d, 2H, J=9Hz);

MS(ES):m/z 290.1$(M+H)^+$.

Example 31

Methyl 3-hydroxy-2-[(4-methoxybenzenesulfonyl)-(2-nitrobenzyl) amino]propionate



To a solution of methyl 3-hydroxy-2-(4-methoxybenzenesulfonylamino)-propionate (15.0 g 51.85 mmol) in N,N-dimethylformamide (125 ml), cooled in an ice bath, was added, portionwise, NaH (2.29 g 57.03 mmol, 60% in oil). The mixture was stirred at 0°C for 20 minutes and then a solution of 2-nitrobenzyl bromide (12.32 g 57.03 mmol) in dry N,N-dimethylformamide (25 ml) was added, dropwise. The solution was stirred at room temperature for 48 hours and diluted with ethyl acetate (500 ml) and water. The organic layer was separated and the aqueous layer extracted with additional f ethyl acetate (250 ml). The combined organic layers were washed with water (200 ml), 1 N sodium bicarbonate (200 ml), saturated sodium chloride (200 ml) and dried over sodium sulfate The solvent was removed *in vacuo* and the residual solid was triturated with ethyl acetate, cooled and filtered to give 13.5 g (61%) of white crystals, mp 127-129°C.

Analysis for $C_{18}H_{20}N_2O_8S$:

Calc'd: C,50.9; H,4.8; N,6.6;

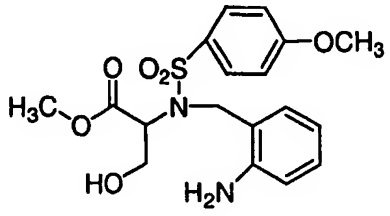
Found: C,50.9; H,4.8; N,6.5;

^{1}H NMR(300 MHz, $CDCl_3$): δ 2.06(m, 1H), 3.51(s, 3H), 3.89(s, 3H), 3.92(m, 2H), 4.59(t, 1H, J= 5.7 Hz); 4.83(d, 1H, J=18Hz); 4.96(d, 1H, J=18Hz), 6.96(d, 2H, J=6.9Hz), 7.43(m,1H), 7.69(m, 1H), 7.76(d, 2H, J=6.8Hz), 7.97(d, 1H, J=6), 8.03 (d, 1H, J=9Hz);

MS(ES):m/z 425.2$(M+H)^+$.

Example 32

Methyl 2-[(2-aminobenzyl)-(4-methoxybenzenesulfonyl)amino]-3-hydroxypropionate



To a mixture, under nitrogen, of methyl 3-hydroxy-2-[(4-methoxybenzene-sulfonyl)-(2-nitrobenzyl)amino]propionate (1.5 g, 3.53 mmol) in dry ethanol (5 ml) was added ammonium formate (1.12 g ,17.69 mmol) followed by the addition of 10% palladium on carbon (0.50 g). The mixture was stirred overnight at room temperature and then heated at 80°C for 2 hours. The mixture was filtered through diatomaceous earth and the filtrate concentrated to dryness *in vacuo* to give a semisolid. Trituration with ethyl acetate gave 0.65 g (47%) of white crystals, m.p. 138-140°C.

Analalysis. for $C_{18}H_{22}N_2O_6S$:

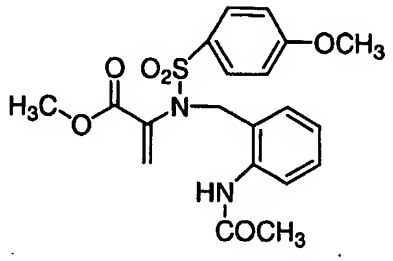
Calc'd: C,54.8; H,5.6; N,7.1;

Found: C,53.0; H,5.6; N,6.8;

^{1}H NMR(300 MHz, $CDCl_3$): δ 1.6(broad, 1H), 3.29(dd, 1H, J=6Hz), 3.56(s, 3H), 3.78(m, 1H), 3.89(s, 3H); 4.2(d, 1H, J=15Hz); 4.62(d, 1H, J=15Hz), 4.71(m, 1H), 6.67(d, 2H, J=6Hz), 6.98(d,1H, J=6Hz), 7.01(m, 2H), 7.12(m, 1H), 7.84(m, 2H); MS(ES):m/z 395.3$(M+H)^+$.

Example 33

Methyl 2-[(2-acetylaminobenzyl)-(4-methoxybenzenesulfonyl)-amino]acrylate



A mixture of methyl 2-[(2-aminobenzyl)-(4-methoxybenzenesulfonyl)amino]-3-hydroxypropionate (8.0 g, 20.28 mmol) in methylene chloride (60ml) was cooled to 0°C and triethylamine (12.69 ml, 91.1 mmol) in methylene chloride (25ml)was added, followed by the addition of acetyl chloride (4.34 ml, 60.84 mmol). The mixture was stirred at room temperature overnight and diluted with methylene chloride. The mixture was washed with water, 2N citric acid, saturated sodium chloride and then dried with anhydrous sodium sulfate. The solvent was removed *in vacuo* to give 8.6 g of a yellow oil.

Analysis. for $C_{20}H_{22}N_2O_6S$:

Calc'd: C,57.40; H,5.30; N,6.69;

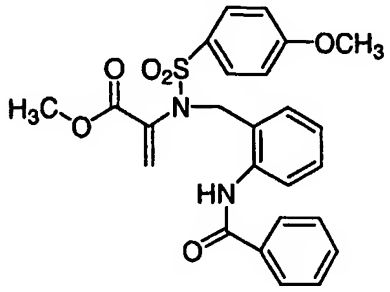
Found: C,55.34; H,5.19; N,6.02;

^{1}H NMR(300 MHz, $CDCl_3$): δ 2.31(s, 3H), 3.67(s, 3H), 3.91(s, 3H), 4.44(s, 2H), 5.46(s, 1H); 6.27(s, 1H); 6.82(d, 1H, J=6.6Hz), 7.02(m, 1H), 7.03(d, 2H, J=6Hz), 7.28(m,1H), 7.77(d, 2H, J=6Hz), 8.05(d, 1H, J=8Hz), 8.6(br, 1H);

MS(ES):m/z 418.9$(M+H)^+$.

Example 34

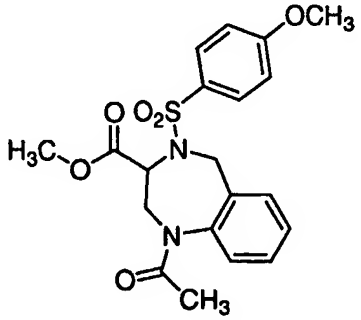
2-[(2-Benzoylamino-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-acrylic acid methyl ester



The procedure of Example 33 was followed using the product from Example 32 (500 mg, 1.268 mmol), triethylamine (0.884 ml, 6.34 mmol), and benzoyl chloride (0.324 ml, 2.79 mmol) in methylene chloride (60 ml) to give 620 mg (100%) of the product.
^{1}H NMR(300 MHz, $CDCl_3$): δ 3.5(s, 3H), 3.89(s, 3H), 4.48(s, 2H), 5.37(s, 1H); 6.25(s, 1H); 6.8(m, 1H), 6.99(m, 3H), 7.38(m, 1H), 7.56(m, 3H), 7.72(m, 2H), 8.18(m, 3H), 9.29(s, 1H).
MS (ES):m/z 480.9 (M+H).

Example 35

Methyl 1-acetyl-4-(4-methoxybenzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylate



To a solution of methyl 2-[(2-acetylamino-benzyl)-(4-methoxybenzenesulfonyl) amino]acrylate (8.40 g, 20.07 mmol) in anhydrous

methanol (5ml) was added anhydrous sodium bicarbonate (2.19 g, 26.09 mmol) and the mixture was stirred at room temperature overnight. Anhydrous sodium bicarbonate (2.2g) was added and the mixture was stirred for 18 hours, heated to 50 °C for three hours and the solvent removed *in vacuo*. The residue was dissolved in water and ethyl acetate. The organic layer was separated, washed with saturated sodium chloride and dried with anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue dried *in vacuo* to give 6.64 g of white crystals, m.p. 150-155°C.

Analysis for $C_{20}H_{22}N_2O_6S$:

Calc'd: C,57.40; H,5.30; N,6.69;

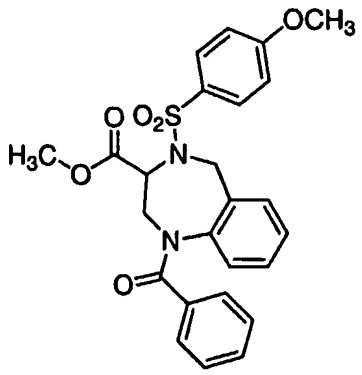
Found: C,57.47; H,5.29; N,6.62;

^{1}H NMR(300 MHz, $CDCl_3$): δ 1.82(s, 3H), 2.93(dd, 1H, J=12Hz), 3.68(s, 3H), 3.84(s, 3H), 4.61(d, 2H, J=15Hz); 4.93(d, 1H, J=15Hz); 5.12(d, 1H, J=15Hz), 6.89(d, 2H, J=9Hz), 7.13(dd, 1H, J=6Hz), 7.33(m,2H), 7.48(dd, 1H, J=6Hz), 7.62(d, 2H, J=9Hz);

MS(ES):m/z 419.1$(M+H)^+$.

Example 36

1-Benzoyl-4-(4-methoxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid methyl ester



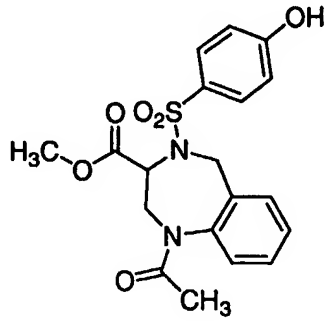
The procedure of Example 35 was followed using the product from Example 34(500 mg, 1.04 mmol) and sodium bicarbonate (114 mg, 1.35 mmoml) in methanol (5 ml) to give 460 mg (92%) of the product.

^{1}H NMR(300 MHz, $CDCl_3$): δ 3.07 (b, 1H), 3.64(s, 3H), 3.84(s, 3H), 4.88(d, 2H, J=14.55Hz); 5.31(b, 1H); 5.57(b, 1H), 6.59(d, 1H, J=7.23Hz), 6.93(m, 3H), 7.15(m,4H), 7.22(m, 1H), 7.38(m, 2H), 7.67(m,2H).

MS (ES):m/z 480.9 (M+H).

Example 37

Methyl 1-acetyl-4-(4-hydroxybenzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]-benzodiazepine-3 -carboxylate



To a 0°C solution of methyl 1-acetyl-4-(4-methoxybenzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylate (9.8 g, 23.42 mmol) in methylene chloride (50ml) was added, dropwise, a 1.0 molar solution of boron tribromide (51.52 ml, 51.52 mmol) in methylene chloride and the mixture was stirred overnight at room temperature. Ice and water were added to the reaction mixture and the insolubles filtered off. The filtrate was diluted with methylene chloride and water. The organic layer was separated, washed with saturated sodium chloride and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give a crude product, which was purified by chromatography on silica gel (hexane:ethyl acetate (l:1)) to give 3.2 g of product as a white foam.

Anal. for $C_{19}H_{20}N_2O_6S$:

Calc'd: C,56.43; H,4.98; N,6.93;

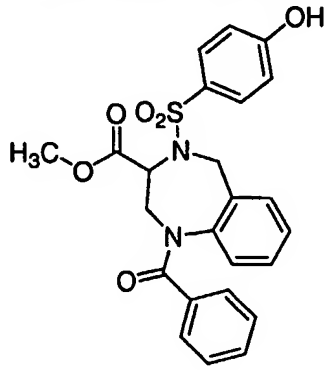
Found: C,55.07; H,4.72; N,6.47;

^{1}H NMR(300 MHz, $CDCl_3$): δ 1.69(br, 1H), 1.89(s, 3H), 2.95(dd, 1H, J=12Hz), 3.56(s, 3H), 4.6(br, 2H); 4.64(d, 1H, J=15Hz); 5.06(d, 1H, J=12Hz), 5.15(d, 1H, J=12Hz), 6.78(d, 2H, J=9Hz), 7.08(t,1H, J=6Hz), 7.28(t, 1H, J=6Hz), 7.41(d, 1H, J=6Hz), 7.5(d, 2H, J=9Hz), 7.6(d, 1H, J=6Hz);

MS(ES):m/z 404.9 $(M+H)^+$.

Example 38

1-Benzoyl-4-(4-hydroxy-benzenesulfonyl)-2,3,4,5-tetrehydro-1H-benzo[e][1,4]diazepine-3-carboxylic acid methyl ester



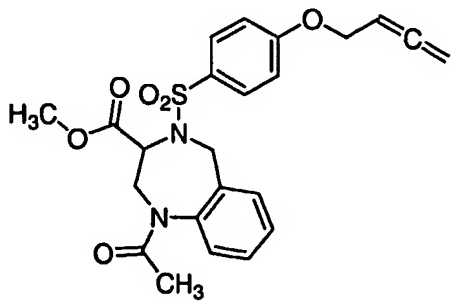
The procedure of Example 37 was followed using the product from Example 36 (9.8 g, 20.4 mmol), 1M solution of boron tribromide (40.8 ml, 40.8 mmol) in methylene chloride (50 ml) to give 4.8 grams (50%) of the product.

^{1}H NMR(300 MHz, $CDCl_3$): δ 3.05 (b, 1H), 3.63(s, 3H), 4.87(b, 2H), 5.28(b, 1H), 5.55(b, 1H); 6.6(b, 2H), 6.82(d, 2H, J=8.7Hz), 6.98(b, 1H), 7.15(b, 4H), 7.23(b, 1H), 7.40(b, 1H), 7.63 (d, 2H, J=7.8).

MS (ES):m/z 466.9 (M+H).

Example 39

Methyl 1-acetyl-4-{[4-but-(2,3-butadienyloxy)phenyl]sulfonyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-3-carboxylate



To a stirred solution of triphenylphosphine (525 mg, 2.0 mmol) in toluene (5ml) was added buta-2,3-diene-1-ol (140 mg, 2.0 mmol) in tetrahydrofuran (5ml) followed by methyl 1-acetyl-4-(4-hydroxybenzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiaze-pine-3-carboxylate (750 mg, 1.85 mmol). To this solution, under nitrogen, was added slowly, dropwise, diethyl azodicarboxylate .(0.315 ml, 2.0 mmol). The mixture was stirred at room temperature overnight and concentrated to dryness *in vacuo*. The residue was purified by chromatography on silica gel preparative plates (ethyl acetate:hexane (1:1)) to give 670 mg of white crystals m. p. 80°C-85°C.

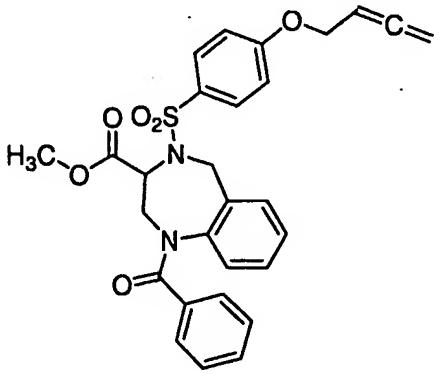
IR(KBR): 3040, 1966, 1748, 1697, 1249, 1028 cm^{-1};

^1H NMR(300 MHz, $CDCl_3$): δ 1.86(s, 3H), 2.96(dd, 1H, J=4.2), 3.67(s, 3H), 4.6(m, 2H); 4.66(br, 1H); 4.69(d, 1H, J=12Hz), 4.89(m, 2H), 5.07(d, 1H, J=12Hz), 5.15(d,1H, J=12Hz), 5.35(m,1H), 6.9(d, 2H, J=6Hz), 7.13(dd, 1H, J=4Hz), 7.33(dd, 1H, J=4Hz), 7.47(d,1H, J=3Hz), 7.63(d, 1H, J=3Hz), 7.67(m, 2H);

MS(ES):m/z 457.2 $(M+H)^+$.

Example 40

Methyl 1-benzoyl-4-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-3-carboxylate



The procedure of Example 39 was followed using the product from Example 38 (650 mg, 1.39 mmol), buta-2-3diene-1-ol (105 mg, 1.5 mmol), triphenylphosphine (393 mg, 1.50 mmol), diethy azodicarboxylate (0.273 ml, 1.50 mmol), and tetrahydofuran (0.4 ml) in toluene (3 ml) to give 300 mg (42%) of the product.

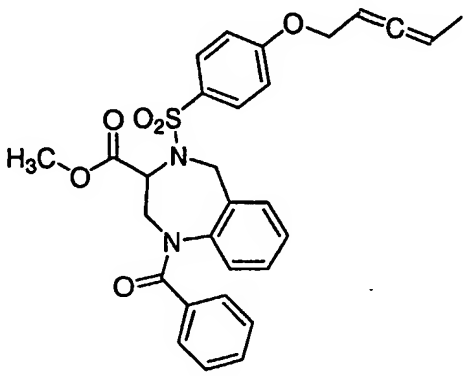
IR(KBR): 2954, 1959, 1750, 1634, 1494, 1329, 1157, 839 cm^{-1};

^1H NMR(300 MHz, $CDCl_3$): δ 3.06(b, 1H), 3.6(s, 3H), 4.59(m, 2H), 4.88(m, 4H); 5.35(m, 2H); 5.56(b, 1H), 6.59(d, 1H, J=5.6Hz), 6.92(m, 2H), 6.97(b,1H), 7.14(m, 5H), 7.24(b, 1H), 7.42(b, 1H), 7.71(b, 2H).

MS (ES):m/z 518.9 (M+H).

Example 41

Methyl 1-benzoyl-4-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-3-carboxylate



The procedure of Example 39 was followed using the product from Example 38 (840 mg, 1.80 mmol), penta-2,3-diene-1-ol (197 mg, 2.34 mmoml), triphenylphosphine (614 mg, 2.34 mmol), diethy azodicarboxylate (0.367 ml, 2.34 mmol) and tetrahydofuran (0.6 ml) in toluene (4 ml) to give 310 mg (32%) of the product.

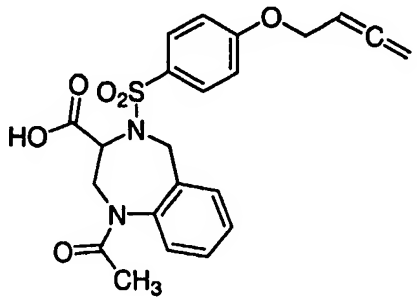
IR(KBR): 2953, 1971, 1749, 1636, 1329, 1157, 767 cm^{-1};

^1H NMR(300 MHz, $CDCl_3$): δ 1.67(m, 3H), 3.06(b, 1H), 3.64(s, 3H), 4.57(m, 2H); 4.87(d, 2H, J=11.2); 5.28(m, 3H), 5.55(b, 1H), 6.58(d, 2H, J=5.55), 6.95(m, 4H), 7.14(m, 5H), 7.43(b, 1H), 7.69(b, 2H).

MS (ES):m/z 532.8 (M+H).

Example 42

1-Acetyl-4-{[4-(2,3-butadienyloxy)phenyl]sulfonyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-3-carboxylic acid



To a solution of methyl 1-acetyl-4-{[4-but(2,3butadienyloxy)phenyl]sulfonyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-3-carboxylate (550 mg, 1.21 mmol) in tetrahydrofuran (1 ml), methanol (1 ml) and . water (5 ml) was added lithium hydroxide hydrate (127 mg, 3.03 mmol). The mixture was stirred at room temperature for 1 hour and concentrated *in vacuo* to dryness. Water was added to the residue and washed with diethyl ether, acidified with 2N hydrochloric acid, extracted with ethyl acetate, washed with saturated sodium chloride and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue dried *in vacuo* to give 525 mg of a white foam.

IR(KBR): 3245, 3040, 1957, 1746, 1624, 1252, 1154, 895 cm^{-1};

^1H NMR(300 MHz, $CDCl_3$): δ 1.88(s, 3H), 3.0(dd, 1H, J=4.2Hz), 4.53(m, 2H), 4.66(m, 2H); 4.86(m, 2H,); 5.13(d, 1H, J=15Hz), 5.37(m, 2H), 6.52(b,1H), 6.84(d, 2H, J=15Hz), 7.12(m,1H), 7.35(m,1H), 7.46(m,1H), 7.55(m, 1H), 7.65(m, 2H);

Analysis. for $C_{22}H_{22}N_2O_6S$:

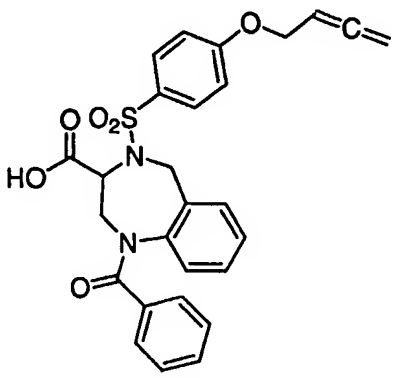
Calcl'd: C, 59.72, H, 5.01; N, 6.33;

Found: C, 57.00; H, 5.43: N, 6.85;

MS(ES):m/z 443.2 $(M+H)^+$.

Example 43

1-Benzoyl-4-(4-buta-2,3-dienyloxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-3-carboxylic acid



The procedure of Example 42 was followed using the product from Example 40 (270 mg, 0.521 mmol), lithium hydroxide (55 mg, 1.3 mmol) in water (0.4 ml), methanol (1 ml) and tetrahydrofuran (1 ml) to give 260 mg (99%) of the product.

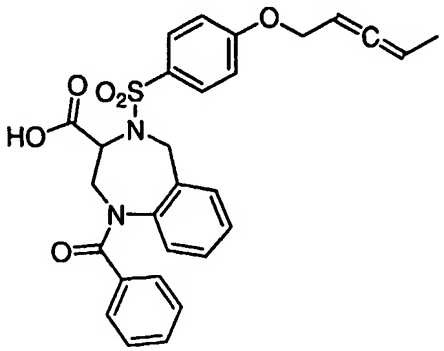
IR(KBR): 3390, 2939, 1957, 1741, 1594, 1495, 1155, 1093, 833 cm^{-1};

^1H NMR(300 MHz, $CDCl_3$): δ 3.06(b, 1H), 3.05-3.7(b, 1H), 4.5(m, 2H); 4.83(b, 2H,); 4.89(m, 2H), 5.18(b, 1H), 5.36(m, 1H), 5.65 (b,1H), 6.57(d, 1H, J=5.6Hz), 6.89 (m, 2H), 6.98(b, 1H); 7.13(m, 5H), 7.28(b,1H),7.43(b, 1H), 7.67(d, 2H, J=5.6.

MS (ES):m/z 502.9 (M-H).

Example 44

1-Benzoyl-4-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-3-carboxylic acid



The procedure of Example 42 was followed using the product from Example 41 (280 mg, 0.526 mmol), lithium hydroxide (55 mg, 1.32 mmol) in water (0.4 ml), methanol (1 ml) and tetrahydrofuran (1 ml) to give 260 mg (95%) of the product.

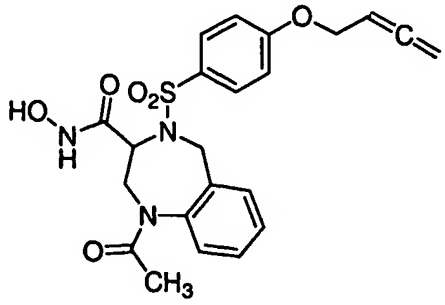
IR(KBR): 3436, 2945, 1969, 1748, 1595, 1495, 1317, 1154, 808 cm^{-1};

^1H NMR(300 MHz, $CDCl_3$): δ 1.67(m, 3H), 2.2-2.9(b, 1H), 3.02(b, 1H), 4.56(m, 2H); 4.83(b, 2H); 5.26(m, 3H), 5.65(b, 1H), 6.57(d, 2H, J=5.7), 6.94(m, 3H) 7.14(m, 4H), 7.26(m, 2H), 7.43(b, 1H), 7.67(d, 2H, J=5.7).

MS (ES):m/z 516.9 (M-H).

Example 45

1-Acetyl-4-{[4-(2,3-butadienyloxy)phenyl]sulfonyl}-N-hydroxy-2,3,4,5-tetrahydro-1H-1,4- benzodiazepine-3-carboxamide



To a stirred solution of 1-acetyl-4-{[4-(2,3-butadienyloxy)phenyl]sulfonyl}-2,3,4,5-tetrahydro-1H-1,4- benzenediazepine-3-carboxylic acid(400 mg, 0.90 mmol) in methylenen chloride (3 ml) and dimethylformamide (1 ml) was added 1-hydroxybenzo-triazole (147 mg, 1.08 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (225 mg, 1.18 mmol). The solution was stirred for 1 hour and hydroxylamine (477 µl, 7.23 mmol, 50% solution in H_2O) was added. The reaction was stirred at room temperature for 24 hours, diluted with methylene chloride, washed with water and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel preparative plates (10% MeOH in EtOAc) to give 228 mg of a white foam.

IR(KBR): 3180, 2962, 1956, 1660, 1494, 1260, 1153, 1028, 802 cm^{-1};

^1H NMR(300 MHz, DMSO-d_6): δ 1.73(s, 3H), 4.62(m, 2H), 4.85(br, 4H,) 4.99(m, 2H); 5.18(br, 1H), 5.48(m, 1H), 6.99(d, 2H, J=8Hz), 7.2(br,2H), 7.59 (m ,4H), 9.0(br, 1H), 11.0(br, 1H);

Analysis for $C_{22}H_{23}N_3O_6S$

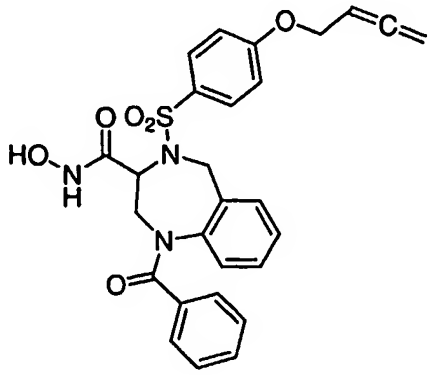
Calc'd: C, 57.76; H, 5.07; N, 9.18;

Found: C, 58.98; H, 5.55; N, 7.78;

MS(ES):m/z 458.2 (M+H)+.

Example 46

1-Benzoyl-4-(4-buta-2,3-dienyloxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-3-carboxylic acid hydroxyamide



The procedure of Example 45 was followed using the product from Example 43 (230 mg, 0.456 mmol), 1-hydroxybenzotriazol (111 mg, 0.821 mmol), 1-[3-(dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride (157 mg, 0.821 mmol), hydroxylamine in water 50% solution (0.251 ml, 4.1 mmol) in dimethylformamide (3 ml) to give 95 mg (40%) of the product.

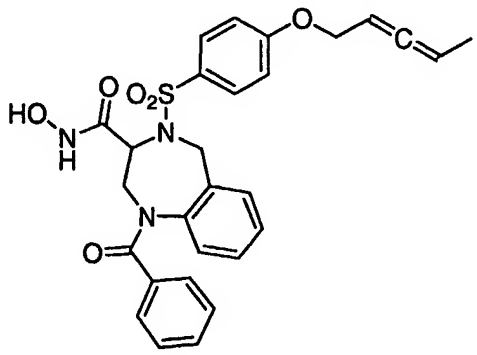
IR(KBR): 3224, 2962, 1956, 1643, 1494, 1323, 1154, 766 cm^{-1};

^1H NMR(300 MHz, DMSO-d_6): δ 3.32(b, 1H), 4.64(m, 2H), 4.78(br, 2H,) 5.0(m, 2H); 5.26(br, 1H), 5.5(m, 2H), 6.5(b, 2H), 6.89(br,1H), 7.06 (m, 2H), 7.28(m, 5H), 7.7(b,2H), 8.97(br, 1H), 11.0(br, 1H);

MS (ES):m/z 519.8 (M+H).

Example 47

1-Benzoyl-N-hydroxy-4-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-3-carboxamide



The procedure of Example 45 was followed using the product from Example 44 (230 mg, 0.444 mmol), 1-hydroxybenzotriazol (72 mg, 0.533 mmol), 1-[3-(dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride (111 mg, 0.579 mmol), hydroxylamine in water 50% solution (0.217 ml, 3.55 mmol) in dimethylformamide (3 ml) to give 130 mg (55%) of the product.

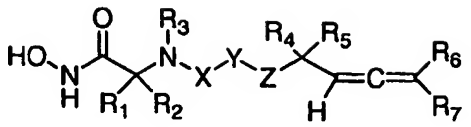
IR(KBR): 3220, 2962, 1968, 1645, 1494, 1323, 1261, 1154, 801 cm^{-1};

^1H NMR(300 MHz, DMSO): δ 1.59(m, 3H), 4.62(m, 3H), 4.79(b, 3H); 5.34(m, 3H), 6.5(b, 1H), 7.06(m, 4H), 7.22(m, 6H), 7.71(b, 2H), 8.96(b, 1H), 11.0(b. 1H)

MS (ES):m/z 531.8 (M-H).

What is claimed:

1. A compound of Formula (I):



(I)

wherein:

X is -S-, -SO-, $-SO_2-$ or $-P(O)-R_8$;

Y is aryl or heteroaryl, with the proviso that X and Z may not be bonded to adjacent atoms of Y;

Z is -O-, -NH-, $-CH_2-$ or -S-;

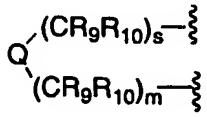
R_1 is hydrogen, aryl, heteroaryl, cycloheteroalkyl, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms;

R_2 is hydrogen, aryl, heteroaryl, cycloalkyl of 3 to 6 carbon atoms, C_5-C_8 cycloheteroalkyl, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms;

R_1 and R_2, taken together with the atoms to which they are attached, may form a 3 to 7 membered cycloalkyl or cycloheteroalkyl ring, which are as herein below defined;

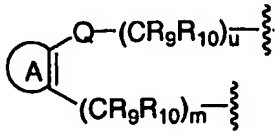
R_3 is hydrogen, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms;

or R_1 and R_3, together with the atoms to which they are attached, may form a 5 to 8 membered ring wherein R_1 and R_3 represent divalent moieties of the formulae:



;

and



A is aryl or heteroaryl;

Q is a C-C single or double bond, -O-, -S-, -SO-, $-SO_2$-, $-NR_{11}$, or $-CONR_{12}$;

s is an integer of 0 to 3;

u is an integer of 1 to 4;

m is an integer of 1 to 3;

R_4 and R_5 are each, independently, hydrogen or alkyl of 1 to 6 carbon atoms;

R_6 and R_7 are each, independently, hydrogen, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, aryl, heteroaryl or cycloheteroalkyl;

or R_6 and R_7, together with the atom to which they are attached, may form 3 to 7 membered cycloalkyl or cycloheteroalkyl ring;

R_8 is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, aryl or heteroaryl;

R_9 and R_{10} are each, independently, selected from H, $-OR_{13}$, $-NR_{13}R_{14}$, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, aryl, heteroaryl, $-COOR_{13}$; or $-CONR_{13}R_{14}$; or R_9 and R_{10} taken together form a C_3-C_6-cycloalkyl of 3 to 6 carbon atoms or a cycloheteroalkyl ring; or R_9 and R_{10} taken together with the carbon to which they are attached, form a carbonyl group;

R_{11} is hydrogen, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, cycloheteroalkyl of 3 to 6 carbon atoms, aryl, heteroaryl, $-S(O)_nR_{13}$, $-COOR_{13}$, $-CONR_{13}R_{14}$, $-SO_2NR_{13}R_{14}$ or $-COR_{13}$, and n is an integer of 0 to 2;

R_{12} is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms or cycloalkyl of 3-6 carbon atoms; and

R_{13} and R_{14} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl or - cycloheteroalkyl; and wherein - $NR_{13}R_{14}$ may form a pyrrolidine, piperidine, morpholine, thiomorpholine, oxazolidine, thiazolidine, pyrazolidine, piperazine, or azetidine ring;

and in the values above:

said aryl group having 6-10 carbon atoms and being optionally mono-, di- or tri substituted;

said heteroaryl is a 5 to 10 membered mono- or bicyclic ring having from 1 to 3 heteroatoms selected from -N-, $-NR_{11}$, -S- and -O- which is optionally mono- or di- substituted; and

said alkyl, alkenyl, alkynyl, cycloalkyl groups being optionally mono or poly substituted;

said substituents of aryl, heteroaryl, alkyl, alkenyl, alkynyl or cycloalkyl being the same or different selected from:

halogen, alkyl of 1 to 6 carbon atoms; alkenyl of 2 to 6 carbon atoms; alkynyl of 2 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, $-OR_8$, -CN, $-COR_8$, perfluoroalkyl of 1 to 4 carbon atoms, -O-perfluoroalkyl of 1 to 4 carbon atoms, $-CONR_{13}R_{14}$, $-S(O)_nR_{13}$, $-OPO(OR_{13})OR_{14}$, $-PO(OR_{13})R_{14}$, $-OC(O)NR_{13}R_{14}$, $-C(O)NR_{13}OR_{14}$, $-COOR_{13}$, $-SO_3H$, $-NR_{13}R_{14}$, $-N[(CH_2)_2]_2NR_{13}$, $-NR_{13}COR_{14}$, $-NR_{13}COOR_{14}$, $-SO_2NR_{13}R_{14}$, $-NO_2$, $-N(R_{13})SO_2R_{14}$, $-NR_{13}CONR_{13}R_{14}$, $-NR_{13}C(=NR_{14})NR_{13}R_{14}$, $-NR_{13}C(=NR_{14})N(SO_2R_{13})R_{14}$, $NR_{13}C(=NR_{14})N(C=OR_{13})R_{14}$ -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_{13}R_{14}$, phenyl, heteroaryl or cycloheteroalkyl;

said cycloheteroalkyl group is a 5 to 8 membered saturated or unsaturated mono or bi-cyclic ring having 1 or 2 heteroatoms independently selected from -N-, $-NR_{11}$, -S- or -O- and is optionally mono- or di –substituted, the same or different, by alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, heteroaryl and cycloheteroalkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein X is $-SO_2-$.

3. A compound according to claim 1 or claim 2 wherein Y is aryl.

4. A compound according to claim 3 wherein Y is phenyl.

5. A compound according to any one of claims 1 to 4 wherein Z is oxygen.

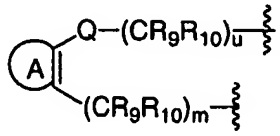
6. A compound according to any one of claims 1 to 5 wherein R_4 and R_5 are hydrogen.

7. A compound according to any one of claims 1 to 6 wherein R_6 is hydrogen.

8. A compound according to any one of claims 1 to 7 wherein R_7 is hydrogen or methyl.

9. A compound according to any one of claims 1 to 8 wherein R_2 is isopropyl.

10. A compound according to any one of claims 1 to 8 wherein R_1 and R_3 represent a divalent moiety of the formula:

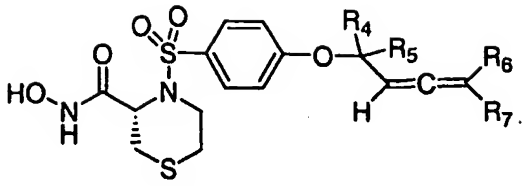


;

wherein Q is NR_{11} , and u and m are 1 and A is phenyl.

11. A compound according to any one of claims 1 to 8 wherein R_1 and R_3 together with the atoms to which each is attached form a thiomorpholine ring.

12. A compound according to claim 11 wherein the absolute stereochemistry is shown by the formula:



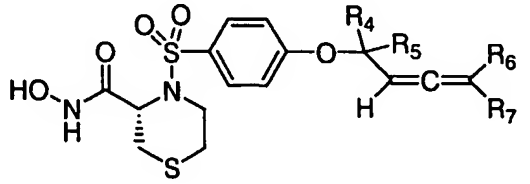
or a pharmaceutically acceptable salt thereof.

13. A compound according to claim 1 wherein Y is aryl and X is $-SO_2-$ and Z is oxygen, R_4, R_5 and R_6 are hydrogen, R_7 is hydrogen or methyl and R_2 is isopropyl.

14. A compound according to claim 1 or claim 13 wherein Y is aryl and R_1 and R_3 together with the atoms to which each is attached form a thiomorpholine ring or a pharmaceutically acceptable salt thereof.

15. A compound according to Claim 13 or claim 14 wherein Y is phenyl.

16. A compound according to claim 15 wherein the absolute stereochemistry is shown by the formula:



or a pharmaceutically acceptable salt thereof.

17. A compound according to claim 1 which is one of the following:
2-({[4-(2,3-Butadienyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-methylbutanamide,
2-[{[4-(2,3-Butadienyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxy-3-methylbutanamide,
N-Hydroxy-3-methyl-2-({[4-(2,3-pentadienyloxy)phenyl]sulfonyl}amino)butanamide,
N-Hydroxy-3-methyl-2-(methyl{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-amino)butanamide,
(3S)-4-{[4-(2,3-Butadienyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide,

(3S)- N-Hydroxy-2,2-dimethyl-4-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-3-thiomorpholinecarboxamide,
1-Acetyl-4-{[4-(2,3-butadienyloxy)phenyl]sulfonyl}-N-hydroxy-2,3,4,5-tetrahydro-1H-1,4- benzodiazepine-3-carboxamide,
1-Benzoyl-4-(4-buta-2,3-dienyloxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-3-carboxylic acid hydroxyamide and
1-Benzoyl-N-hydroxy-4-{[4-(2,3-pentadienyloxy)phenyl]sulfonyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-3-carboxamide;
or a pharmaceutically acceptable salt thereof.

18. A method of treating a pathological condition mediated by TNF-α converting enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula (I) as defined in any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof.

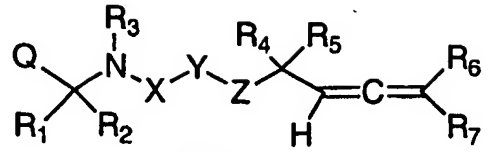
19. A method of treating a pathological condition mediated by matrix metalloproteinases in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula (I) as defined in any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof.

20. The method of claim 18 or claim 19 wherein the condition treated is rheumatoid arthritis, osteoarthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease, degenerative cartilage loss, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV.

21. A pharmaceutical composition comprising a compound having the formula (I) as claimed in any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

22. A process for preparing a compound of formula (I) as claimed in claim1 which comprises:

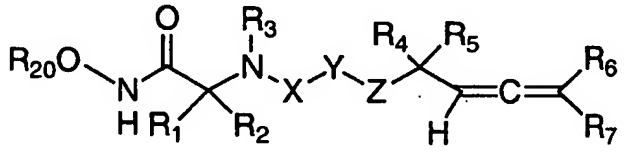
reacting a compound of formula V:



(V)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, X, Y and Z are as defined in claim 1 and Q is COOH or a reactive derivative thereof, with hydroxylamine to give a corresponding compound of formula (I); or

c) deprotecting a compound of formula VI:



(VI)

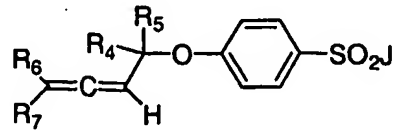
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, X, Y and Z are as defined in claim 1, and R_{20} is a protecting group, to give a compound of formula (I);

c) resolving a mixture (e.g racemate) of optically active isomers of a compound of formula (I) to isolate one enantiomer or diastereomer substantially free of the other enantiomer or diastereomers;

or

d) acidifying a basic compound of formula (I) with a pharmaceutically acceptable acid to give a pharmaceutically acceptable salt.

23. A compound of formula



wherein R_4, R_5, R_6, and R_7 are as defined in claim 1 and J is F, Cl or Br.

INTERNATIONAL SEARCH REPORT

Inte... ...al Application No
PCT/US 02/34904

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C311/29 C07D279/12 C07D243/14 A61K31/48 A61K31/54
A61K31/5513 A61P19/02 C07C309/87

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 225 311 B1 (J.L. LEVIN, ET AL) 1 May 2001 (2001-05-01) column 203, line 56 - line 64; claim 1; tables 1-14	1,18-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 2003	03/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/US 02/34904

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ›nal Application No
PCT/US 02/34904

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6225311 B1	01-05-2001	US 2003008849 A1	09-01-2003
		US 6277885 B1	21-08-2001